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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JUNE 1940

ADRENAL INSUFFICIENCY[1]*

ROBERT F. LOEB

Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York

CLINICAL PICTURE

ADRENAL cortical insufficiency in man, as represented by Addison's disease, may develop at any age although it occurs most frequently between the ages of 20 and 50 years. It is characterized in most cases by the insidious development and progression of asthenia and fatiguability although not infrequently adrenal crises may give the first evidence of the disease. The symptoms are usually accompanied by the appearance of brownish pigmentation which increases over a period of months and which may be blotchy in its distribution or generalized. It is most intense on the knees, nipples or in the axillary folds as well as on the exposed parts, particularly the knuckles. The most characteristic feature of the pigmentation is the appearance of small brown or gray-black patches on the lips, gums, tongue or cheeks. In some cases, pigmentation may be entirely absent while in others it may exist in combination with numerous areas of depigmentation (Figs. 1 and 2).

Gastrointestinal symptoms are usually present and occasionally dom-

[1] Delivered October 27, 1939 at the Twelfth Graduate Fortnight of The New York Academy of Medicine.
* Many of the studies presented were made in collaboration with Drs. D. W. Atchley, J. Stahl, J. W. Ferrebee and C. A. Ragan, Jr.

Fig. 1—The presence of both pigmentation and depigmentation in a patient with Addison's disease.

Fig. 2—Depigmentation associated with profound pigmentation in another Addisonian patient.

inate the disease picture. The appetite is almost invariably capricious and periods of anorexia occur with great regularity. This latter symptom is associated with infrequent bouts of vomiting which usually take place in the morning. During crises, emesis increases; there may be "coffee-ground" vomitus and finally there may be complete gastric intolerance. Abdominal pain is often present and may suggest disease of the biliary tract or even peptic ulcer. Diarrhea is only an occasional complaint.

Hypotension is almost always present in Addisonian patients whose symptoms are sufficiently marked to cause them to seek medical aid. The systolic pressure is usually less than 100 mm.Hg. but it may and frequently does rise during excitement to higher levels for short periods of time. During severe crises, the systolic pressure may fall to 50 mm. Hg. or even less and the pulse pressure is often only 10 mm.Hg. The pulse is characteristically small in volume although it is occasionally full and soft. Under the influence of pain or emotional stress the pressure, even during crises, may momentarily rise to normal levels.

In a few instances hypoglycemia, with the symptoms and signs which characterize that state, dominates the clinical picture in Addison's disease. In most cases hypoglycemic episodes appear relatively late in the disease, particularly among patients already under treatment with salt.

The adrenal crisis consists of an abrupt increase in the intensity of the disease manifestations, notably weakness, prostration, hypotension, gastrointestinal symptoms and transient neurological disorders which may include confusional states as well as abnormal reflexes. In the course of a few hours or a few days, either spontaneously or as a result of an acute infection, or because of a surgical procedure, a severe emotional upset or the withdrawal of salt from the diet, the tempo of the disease process accelerates with alarming rapidity. The patient frequently dies during the crisis if energetic therapy is not instituted promptly, and occasionally dies despite the best possible treatment. The terminal crisis is often associated with a rise of temperature to 104 or 105° for which no adequate explanation may be found.

Disturbances in Physiology

Thomas Addison, in 1855, pointed out for the first time that "universal disease of the capsules" is incompatible with life and stated that

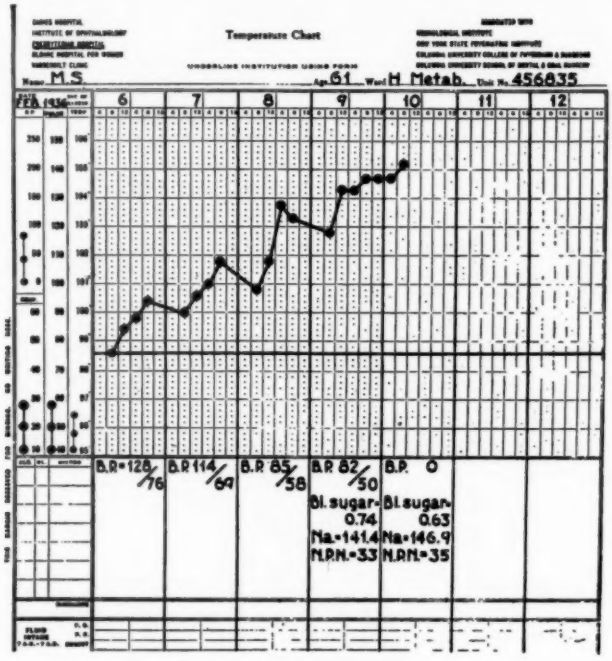

Fig. 3—Typical fatal terminal rise in temperature without adequate explanation at autopsy.

aside from this observation the function of these structures "is almost, or altogether, unknown." At the same time, Addison predicted that the further study of disease of the adrenal glands might lead to some understanding of their physiological activity. This prophecy has in recent years been amply fulfilled and it is to a consideration of problems of the functions of the cortex of the adrenal glands and the treatment of adrenal insufficiency that I should like to call your attention.

Salt and Water Metabolism

Among the most important disturbances resulting from insufficiency of the adrenal cortex are those related to electrolyte and water metabolism. Baumann and Kurland[1] and Marine and Baumann[2] in 1927 demonstrated that the ablation of the adrenal glands in animals resulted in a decrease in the *sodium concentration* in the serum and an increase in

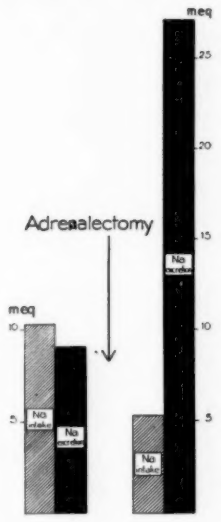

Fig. 4—Effect of adrenalectomy upon the urinary excretion of sodium in the dog. The great loss of sodium which follows adrenalectomy takes place through the kidneys.

serum potassium. They also showed that the injection of sodium chloride prolonged life more than did salts of other cations or solutions of glucose. In 1932, we found at the Presbyterian Hospital[3,4,5] in patients with decompensated adrenal insufficiency (adrenal crises) that the state of dehydration in these individuals was associated with a constant decrease in the concentration of sodium in the blood and a less constant increase in potassium. The concentration of sodium may fall from a normal value of about 140 m. eq. per l. to a level of about 100 m. eq. per l. and potassium may rise to about 10 m. eq. per l., a little more than double the normal concentration. The decrease in serum sodium is accompanied by a corresponding drop in chloride, bicarbonate, or both. We also pointed out the importance of the use of sodium salts and water in correction of these disorders and showed that an adrenal crisis might be induced by the simple process of the withdrawal of the sodium ion from the diet. The changes observed in the first patient of this study are shown in Table 1. Finally, we were able to demonstrate that the

TABLE 1

CORRELATION OF BLOOD CHANGES WITH SALT FEEDING AND SALT WITHDRAWAL IN A PATIENT WITH ADDISON'S DISEASE

Date	*Na*	*K*	*Cl*	*HCO_3*	*Non-Protein Nitrogen*	*Blood Pressure*	*Remarks*
	m. eq. per l.	m. eq. per l.	m. eq. per l.	m. eq. per l.	mg. per 100 cc.		
July 19 1932	123.5	5.3	88.6	21.8	39.0	85/55	Blood taken shortly after admission. Profound weakness and vomiting.
July 26	107.8	7.1	72.7	21.5	45.0	65/48	Critically ill. Almost in extremis. No therapy up to this time.
Aug. 2	133.0	5.1	93.8	27.5	20.6	84/60	Treated with a single dose of Eschatin and then NaCl daily. No more vomiting, sitting up.
Nov. 14	139.9	4.6	107.3	24.3	20.0	112/74	Up and about at home, doing part of housework. Eats 7 gms. of NaCl daily plus diet. Slight puffiness of eyelids.
Jan. 24 1933	126.8	5.7	92.3	21.2	35.0	86/60	After 7 days salt-poor diet, weak and vomiting frequently. Confined to bed.
Jan. 30	138.0	5.0	103.5	25.9	25.0	122/80	After no further treatment except NaCl added to diet and given by rectum. No vomiting. Much stronger.

decrease in sodium concentration in the blood serum was associated with an increase in the excretion of this base and water by the kidneys, perhaps as a result of a decrease in their reabsorption by the renal tubules. The order of magnitude of the sodium excretion suggested that it was lost from the interstitial fluid of the tissues as well as from the blood. Harrop[6, 7] confirmed these observations and, simultaneously with Allers and Crandall,[8] showed that completely adrenalectomized dogs could be maintained in good health for many months without the use of cortical extract if given large amounts of sodium chloride to which was added sodium bicarbonate or citrate. *Thus, the presence of a defect in sodium metabolism in adrenal insufficiency in man and animals has been clearly established and it has been shown that the administration of sodium salts and water may re-establish adrenal compensation.*

A reduction in the sodium concentration in the body alone without a concomitant decrease in blood volume and interstitial fluid does not, however, give rise to the picture of adrenal insufficiency. For example, in a patient with mild adrenal insufficiency who was maintained in moderately good health by the oral administration of salt and water by Willson and Sunderman,[9] the restriction of water ingestion resulted in the precipitation of a crisis accompanied by a sharp decrease in blood plasma volume. It is noteworthy that the serum sodium level, which was abnormally low before water restriction, rose to normal with the onset of the crisis as a result of a decrease in the water content of the plasma. This finding aids in the explanation of the observation of Winter et al.,[10] who induced rapidly fatal adrenal insufficiency in cats by interrupting the supraopticohypophyseal tract and subsequently removing the adrenal glands. In these animals with diabetes insipidus, adrenal insufficiency developed despite the fact that the sodium content of the blood remained normal and while the potassium content increased. It is probable that in these cats death resulted from shock associated with a decrease in plasma volume.

Potassium Metabolism

Accompanying the decrease in serum sodium concentration and the loss of water with the development of adrenal insufficiency there is usually, as has been stated, *an increase in the concentration of potassium.* The importance of the abnormality of potassium metabolism in adrenal insufficiency is becoming more and more impressive. Kendall and Allers,[11] as well as Zwemer,[12] have demonstrated the abnormal susceptibility of adrenalectomized animals to the ingestion or injection of small amounts of potassium salts, and Wilder, Snell and their collaborators[13] have indicated the danger attendant upon the ingestion of large amounts of potassium salts by patients with Addison's disease. The latter investigators have shown that one deleterious effect of potassium salts results from the fact that they tend to augment the excretion of the sodium ion. Another reason for the toxic effects resulting from the ingestion of liberal amounts of potassium salts is the retention of potassium in the blood serum above the normal level of 4 to 5 m. eq. per l. This develops, apparently, because of failure to excrete potassium as rapidly as normal.

It has been maintained by some that the increase in potassium in the blood is responsible for the adrenal crisis. This concept appears to be

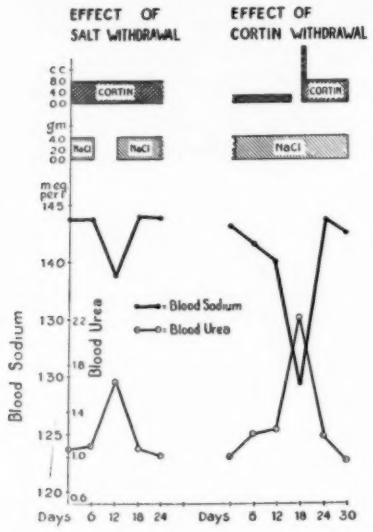

Fig. 5—Qualitative similarity of the effect of the withdrawal of salt and cortin in the adrenalectomized dog. The behavior of potassium parallels that of blood urea.

untenable because, as has been stated, there is often no increase in serum potassium in patients with Addison's disease whereas in other disease states, in which potassium is often retained, e.g., renal insufficiency, the clinical picture of adrenal insufficiency is not present.

Renal Function

In 1916 Marshall and Davis[14] noted an increase in non-protein nitrogen in the blood of adrenalectomized animals and were the first to suggest that the adrenal glands exert an influence on *renal function*. In patients suffering from Addisonian crises there is often some retention of non-protein nitrogen, the highest value observed by us being 102 mg. per 100 cc. This disturbance can be corrected by the administration of salt and water, but even when the sodium concentration reaches a normal level a decrease in the urea clearance may persist. Recent work of Margitay-Becht and Gömöri[15] indicates that this disturbance in renal function results at least in part from a decrease in renal blood flow and in glomerular filtration as measured by creatinine clearance tests.

Studies of Stahl, Kuhlmann and Urban[31] suggest a similar conclusion. In severe adrenal insufficiency, there may also be retention of phosphate and sulphate and a decrease in the formation of urinary ammonia. Whether a decrease in renal blood flow alone accounts for the decrease in ammonia formation or whether a specific disturbance in nitrogen metabolism is responsible for it is not known. It seems certain that the disturbances in sodium and water metabolism are, at least in part, dependent on faulty renal mechanism which results from a lack of cortical hormone. Furthermore, Harrison and Darrow[16] believe that they have demonstrated in adrenal insufficiency a specific disturbance in renal function insofar as the normal regulation of potassium excretion is concerned.

Carbohydrate Metabolism

Since Porges[17] in 1909 first demonstrated the presence of hypoglycemia in patients with Addison's disease as well as in adrenalectomized animals, it has been recognized that a *disturbance in carbohydrate metabolism* exists in adrenal insufficiency. A decrease in glycogen storage has been emphasized repeatedly by Britton and Silvette[18] and the sensitivity of the Addisonian patient to the injection of small doses of insulin is well established. The studies of Britton and those of Long and his associates[19] have demonstrated that glycogen storage in the liver of adrenalectomized and also normal animals is increased by the injection of potent cortical extract or of certain crystalline steroids isolated from the adrenal glands, notably corticosterone in contrast to desoxycorticosterone.

In most patients with Addison's disease there is mild hypoglycemia. Thus, among a group of twenty-three of our patients the fasting blood sugar level at some time was found to be below 80 mg. per cent in sixteen; in nine it was below 70 mg.; and in five there were classical severe hypoglycemic episodes associated with blood sugar levels below 50 mg. per cent. This hypoglycemia cannot be correlated with the concentration of sodium or potassium in the blood. On the other hand, Long[19] has recently presented convincing evidence indicating that, in the rat, at least, certain crystalline substances, obtained from the adrenal cortex, which are active in correcting the salt and water disturbances are also active in their action on carbohydrate metabolism. Kendall[20] has recently presented evidence suggesting that an antagonistic action exists between

insulin and adrenal cortical hormone and that, in the absence of the latter, there is a flow of potassium and glucose to tissue cells similar to that following insulin administration. On the other hand, in the diabetic rat, Kendall reports that the administration of cortical extract increases the urinary excretion of potassium in addition to augmenting glucose elimination as earlier demonstrated by Long.[19] It is Long's[21] contention that the increase in potassium excretion results from the increase in protein breakdown and gluconeogenesis stimulated by certain steroids of the adrenal cortex.

Miscellaneous Disturbances

Certain other physiological disturbances, secondary to the abnormalities of electrolyte and water metabolism, are present in the adrenal crisis and contribute to the picture of dehydration and shock. These include a decrease in plasma volume, a fall in blood pressure to levels of shock, a decrease in blood flow, acrocyanosis and hemoconcentration. Occasionally fatal adrenal insufficiency develops with evidence of hemoconcentration, peripheral vascular collapse and fever but without demonstrable abnormalities of the electrolytes and glucose of the blood. The underlying explanation in these instances remains obscure but dehydration with relative retention of sodium, as in the patient of Willson and Sunderman, may constitute the mechanism involved.

Whereas the decreases in plasma volume and peripheral blood flow as well as disturbances in carbohydrate metabolism constitute factors contributing to the asthenia of the Addisonian patient, it seems likely that certain unknown mechanisms are also involved. This idea is supported by the important observations of Ingle[22] which show that despite the simultaneous treatment of adrenalectomized rats with salt, corticosterone and desoxycorticosterone, the capacity of these animals for muscular work continues at a level strikingly lower than that of sham-operated animals.

A number of neurological disturbances, both focal and diffuse, may occur in the course of adrenal insufficiency. In certain instances these may result from hypoglycemia, in others hypotension and a decrease in cerebral blood flow may play a part. Whether or not other factors may be present is not known.

Hypercalcemia is at times present in adrenal insufficiency and cannot be ascribed to hemoconcentration alone. Bilirubinemia, elevation of

serum phosphatase and retention of bromsulphalein have also been encountered. The reason for these disorders and the mechanism underlying the disturbances of pigmentation in Addison's disease are not understood.

Verzár[23] has recently ascribed the basis for physiological disturbances in adrenal insufficiency to a failure of the important function of phosphorylation. This function among other activities is responsible for the formation of respiratory ferment from its precursor riboflavin, i.e., vitamin B_2 and for the specific absorption of glucose, levulose and fat from the bowel. However, the validity of this attractive hypothesis seems extremely doubtful in the light of recent studies, particularly those of Ferrebee[24] who has shown that the ability to phosphorylate vitamin B_1 is retained in completely adrenalectomized rats.

Treatment

I should like now to consider the problem of the treatment of Addison's disease. The treatment of Addison's disease, like that of diabetes mellitus, should be directed primarily toward (1) the specific replacement of the hormone or hormones lacking, (2) the correction of the physiological disturbances which ensue as a consequence of this endocrine deficiency, and (3) the avoidance of factors known to intensify manifestations of the disease. The nature of the therapy and the vigor with which it must be applied vary tremendously with the phase of the disease present. In the patient whose disease is well compensated, a few general measures such as the avoidance of physical and mental fatigue, the immediate care of even mild acute infections, and the ingestion of a liberal amount of sodium chloride will suffice to maintain moderately good health for periods of months or even years. On the other hand, with the appearance of a crisis, whether it appears in the natural progression of the disease or whether it results from known causes, a number of active therapeutic measures must be applied promptly and intensively in order to combat successfully the grave and often fatal loss of inorganic base with its attendant dehydration and peripheral circulatory collapse. Procrastination or inadequate treatment of the crisis sacrifices patients who might otherwise be restored to a useful existence.

Before proceeding with the discussion of therapy, I should like to digress for a moment to make a plea that the treatment of adrenal insufficiency in man be limited to patients who can be shown to be suffering from that condition. This is meant to be neither trite nor flippant, but

we continue to see a large number of patients, mostly asthenic, tired women, who have received injections of 2 to 3 cc. of certain commercial extracts daily or perhaps once a week. It is unlikely that this treatment does harm but it is certain that it is costly and totally ineffective beyond its action as a placebo. The treatment of cortical adrenal insufficiency is directed primarily at disturbances of water and electrolyte metabolism. If these are not obviously present or if they cannot be made manifest by placing the suspected patient upon a salt-poor regime, under close observation for 1 to 7 days, there can be little or no reason for instituting the treatment of Addison's disease.

With the recognition of the disturbances in electrolyte and water metabolism present in adrenal insufficiency and as a result of the introduction of salt treatment,[4] the unhappy plight of the Addisonian patient was to a certain extent bettered. The introduction of the low potassium diet by Wilder and his colleagues[13] constituted a further theoretical improvement. The preparation of extracts of the adrenal cortex for use in patients gave much promise and in large amounts they have been demonstrated by Thorn and others[25] to have undeniable physiological activity. Nevertheless, I think we will all agree that in doses which patients can afford or tolerate, the results of treatment have by and large been disappointing.

In the past year, the synthesis of desoxycorticosterone by Steiger and Reichstein[26] in Zürich has made available for use in patients a natural steroid of the adrenal cortex which has easily demonstrable physiological activity. While this chemical entity is, as already mentioned, only one of a series of known active steroids in the cortex and while there are other substances of far higher potency not yet identified chemically, this steroid has shown itself to be of extraordinary importance in the treatment of adrenal insufficiency. In addition to this advance of significant practical value we have learned much concerning the nature of the physiological disturbances resulting from adrenal cortical insufficiency by observing the changes brought about by the administration of a single chemical substance, i.e., one of the esters of desoxycorticosterone.

In this country, Thorn[25,27] was the first to use desoxycorticosterone and he has contributed greatly to the practical aspects of the treatment of Addison's disease with the implantation of pellets. His studies have also added to our knowledge of the action of desoxycorticosterone. Our own results are in general agreement with those obtained by him as well

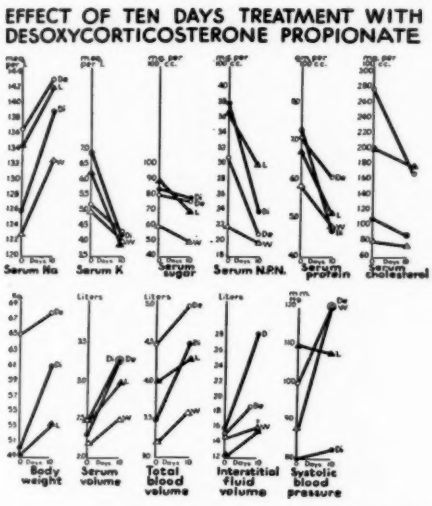

Fig. 6—Effects produced in Addisonian patients in 10 days by a desoxycorticosterone derivative. These patients received *large* doses, i.e., about 190 mg., during initial 10 days of treatment.

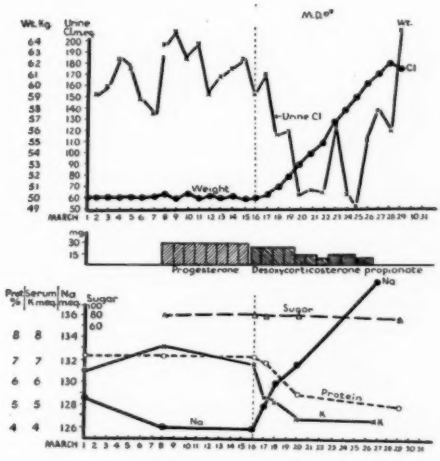

Fig. 7—A comparison of the effects of progesterone and desoxycorticosterone in a patient with Addison's disease.

as those reported by Cleghorn and his associates[28] and amplify those of Levy Simpson[29] in England.

At the Presbyterian Hospital, Drs. Ferrebee, Ragan, Atchley and I[30] have in the past 10 months had eighteen patients with Addison's disease under treatment with esters of desoxycorticosterone furnished by the Roche-Organon laboratories. In our studies we have employed both the acetate and propionate of desoxycorticosterone which have been administered subcutaneously or intramuscularly in peanut oil. Results of the administration of desoxycorticosterone may be summarized as follows:

Salt and Water Metabolism

Desoxycorticosterone esters cause a striking retention of salt and water. The rate of retention of the sodium ion usually exceeds that of water so that as a rule the serum sodium concentration rises to normal and is maintained at normal level as fluid retention continues. In a few instances, water is retained more rapidly than sodium so that the sodium concentration of the blood may actually fall for a few days. In one of our patients with extensive tuberculosis, it was never possible to raise the sodium concentration above 132 m. eq. per l. although the retention of water was sufficient to be associated with pulmonary congestion, hydrothorax, generalized edema and temporary elevation of venous pressure.

The amount of salt and water retained varies greatly in different patients and cannot be correlated with the initial sodium or serum protein concentration or with the initial plasma volume. One of our patients gained 11 kilos in 10 days during which time he received 190 mg. of hormone. In contrast, another patient gained but 2 kilos in 30 days during which time he received 725 mg. of hormone. Both patients received the same amounts of sodium and potassium salts in their diets.

Coincident with the retention of salt and water and with the gain in weight there appears a considerable decrease in the urinary excretion of sodium, chloride and water. For example, in one of our patients the urine output fell from an average of 1500 cc. daily to as little as 410 cc. during the period of administration of 15 mg. of hormone each day. The sodium excretion fell from a level of about 160 m. eq. to 28 m. eq. in 24 hours and the chloride excretion underwent a commensurate change.

As a result of these changes, there is marked increase in extracellular fluid volume as measured by the thiocyanate method. The blood plasma

volume in those patients in whom it was measured increased between 300 and 1200 cc. during the first ten days of treatment with hormone. These changes were in close agreement with decreases in hematocrit and serum protein concentration. In two patients, the serum protein concentration fell from 7.3 to 4.7 and from 5.9 to 4.8 per cent respectively. There were no consistent changes in albumin/globulin ratio associated with this dilution of the blood.

Potassium Excretion

Synthetic desoxycorticosterone esters cause a striking decrease in the concentration of the potassium in the serum and frequently reduce it to abnormally low levels. Thus, in nine out of a group of ten patients, the potassium concentration after treatment was below 4 m. eq. per l., the lower limit of our normal values. In two patients, potassium has reached a level of 2.9 and 2.4 m. eq. per l. respectively.

The urinary excretion of potassium increases regularly on the first day of hormone injection and thereafter it becomes variable. The potassium excretions cannot be satisfactorily correlated with changes in nitrogen excretion as might be expected if the increase were due solely to the destruction of body protein for gluconeogenesis.

Nitrogen Excretion

The non-protein nitrogen level of the serum decreases even when it is within normal limits at the beginning of treatment.

Total nitrogen excretion may not be affected but as a rule there is a slight increase not exceeding 2 grams in the first 2 or 3 days of therapy. Ammonia excretion appeared to increase within 24 hours after administering desoxycorticosterone in the two patients in whom determinations were made before and after treatment.

Blood Calcium and Cholesterol

The serum calcium concentration decreases following the administration of synthetic hormone. This was observed to be true in each of six patients in whom determinations were made before and after 10 days of therapy. This change may be attributed to hemodilution with its attendant decrease in serum albumin concentration.

The cholesterol content of the blood also decreases, at least in part as a result of hemodilution.

Carbohydrate Metabolism

No evidence has been found in our studies to suggest that desoxycorticosterone esters have any effect on carbohydrate metabolism in our patients with Addison's disease. After 10 to 40 days of treatment the fasting blood sugar level is often as low as or even lower than before. In one patient who received the enormous dose of 25 mg. of hormone daily for 30 days the fasting blood sugar level was 74 mg. and 4 hours after the ingestion of 100 grams of glucose it fell to 46 mg. per cent. The respiratory quotients, measured on 2 days before and again on 2 days after 2 weeks of hormone treatment in this patient, were 0.85 and 0.78 respectively, indicating a change of questionable significance. In another patient receiving 10 mg. of hormone daily, severe hypoglycemia with blood sugar levels of 40 and 38 mg. per cent were observed on successive days after 2 weeks of treatment. The dose of hormone in this patient was insufficient to raise the blood sodium to normal though it was adequate to cause excessive fluid retention.

Blood Pressure

The effect of desoxycorticosterone esters on arterial pressure is dramatic even though it does not appear as promptly as do the effects on salt and water metabolism. The blood pressure has reached normal in all of our patients in the course of 2 to 4 weeks and has risen gradually to 175/110, 160/92, 160/110 and 146/108 in four patients. In only one of these patients was there, on the basis of history, evidence of hypertensive vascular disease antedating the onset of Addison's disease.

Pigmentation

No definite effect on pigmentation has been noted in any of our patients beyond that which may be attributed to rehydration.

Complications

In view of the high degree of physiological activity of desoxycorticosterone esters, it could be anticipated that overdosage might result in the appearance of disturbing complications. Indeed, fifteen of eighteen patients developed edema varying from mild and transient puffiness of the face and ankles to massive anasarca. In five patients there developed varying degrees of respiratory distress, a sense of tightness in the chest

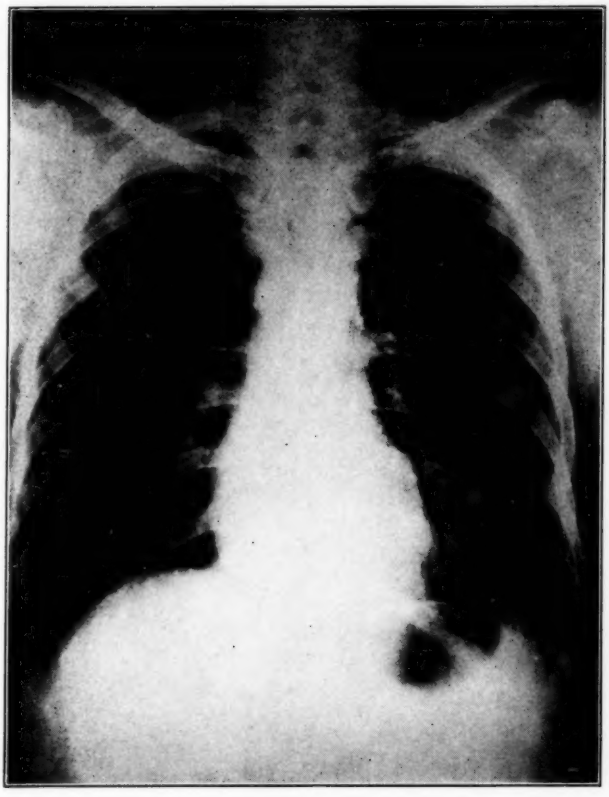

Fig. 8—X-ray of heart of an Addisonian patient before treatment.

associated with x-ray evidence of dilatation of the heart predominantly on the right side. In four of these five patients, there was an elevation of venous pressure which reached levels from 110 mm. to 250 mm. In three in whom determinations were made there was a striking decrease in vital capacity associated with definite evidence of pulmonary congestion on x-ray examination. In four of the five patients developing cardiac dilatation and congestive failure, prompt relief resulted from the limitation of sodium chloride intake to that present in the diet and in certain instances with reduction in the dose of desoxycorticosterone. One patient who had been taking 15 mg. of hormone every other day and had added

Fig. 9—X-ray of heart of the same patient as in Fig. 8 after excessive treatment with desoxycorticosterone acetate and salt.

2 to 3 teaspoons of salt to his diet received some relief from limitation of salt and water and a phlebotomy but succumbed with terminal bronchopneumonia. Autopsy revealed dilation of the heart with mild hypertrophy and a curious swelling of the muscle cells and their nuclei in the right ventricle.

The mechanism for the development of cardiac insufficiency in these patients is not clear. It is certain that it does not result from an increase in arterial pressure alone because in three of our patients congestive failure appeared when the blood pressure was below 110 mm. Hg. A rapid

and extensive increase in circulating blood volume is a possible factor, although in one patient the increased blood volume caused by the hormone was only 300 cc. at the time when the venous pressure was elevated and the symptoms were most marked. The possible relation of the decrease in potassium concentration is inescapable but its significance is not known. There is no evidence of vitamin B_1 deficiency as an etiological factor with the exception of relatively low excretion of thiamin in the urine of some of these patients.

The complications which have been discussed serve to indicate the dangers attendant upon the use of desoxycorticosterone esters and I think that they are of sufficient gravity to justify a warning concerning their indiscriminate or uncontrolled use.

Results of Treatment

It is beyond the scope of this paper to discuss the details of treatment. I might, however, say a few words concerning our experiences. Four out of eighteen patients who have been under treatment with synthetic hormone in the past 10 months have died. One of these succumbed secondary to cardiac insufficiency, as has been stated. Another died with advanced tuberculosis. Two died suddenly at home and information obtained has not been sufficient to interpret the cause of death. One other patient died unexpectedly while under observation in the hospital. She had had mild cardiac insufficiency of the type already described and her blood electrolyte pattern except for slight depression of the potassium level was essentially normal 3 days before death. The night before her death she had a rise in temperature to 103° associated with vomiting and slight sore throat but the next morning, except for mild symptomless hypoglycemia (her blood sugar was 62 mg. per cent), she appeared well. On rounds, she gagged mildly while having her throat examined and fell back on her pillow dead. Autopsy afforded no explanation for her sudden demise. The remaining patients have made extraordinary gains as far as their sense of well-being, their strength, their appetite, their weight, and their outlook on life are concerned. Some are at work and others are, from the point of view of strength, capable of undertaking their normal activities. It must be remembered, however, that the majority of patients with Addison's disease are suffering not only from adrenal insufficiency but also from tuberculosis which offers a therapeutic problem in itself.

The individual hormone requirements of patients with adrenal insufficiency vary widely and our patients appear to need as a maintenance dose between 1 and 10 mg. daily administered in peanut oil under the skin. It seems to us that the dangers of cardiac insufficiency may be greatly diminished if the dose of hormone is sufficiently great so that the patient will not require a salt intake in excess of the normal diet. The treatment of the acute crises requires the parenteral administration of glucose in normal salt solution and the administration probably in most instances of about 25 mg. of hormone daily for a period of 3 or 4 days. The blood sodium level, the arterial pressure, the venous pressure and the patient's general condition must serve as the guides to dosage.

In conclusion it may be reiterated that in recent years a great deal has been learned concerning the nature of the disturbances present in adrenal insufficiency. While many of these appear to be related directly or indirectly to disturbances in electrolyte and water metabolism or to abnormalities in carbohydrate metabolism, there remain innumerable problems which have not been solved.

With the synthesis of desoxycorticosterone there has been made available a valuable therapeutic agent for the correction of disturbances in electrolyte and water metabolism in adrenal insufficiency. This synthetic hormone offers considerable hope for the future of those individuals suffering from Addison's disease, but it seems likely that other substances will become available which will find wider application in the correction of the multiple disorders present.

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THE CUSHING SYNDROME; NEOPLASMS OF THE ADRENAL GLAND*

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WE OWE a great debt to Dr. Harvey Cushing[1] for his careful delineation in 1932 of the clinical syndrome which now bears his name. Such a striking picture could not escape notice and there are earlier references to some of its features. Hippocrates[2] said of Phoetas, wife of Pythias, that she lost her periods, became masculinized and developed a beard. The first definite case is the often misquoted one of William Cooke,[3] who reported, in 1811 under the title "A Case of Internal Hydrocephalus," the findings in a child who presented plethoric obesity, hirsuties and an enlarged clitoris. At postmortem examination there was found a tumor in the region of the right adrenal gland. Although Thornton[4] in 1890 had removed an adrenal tumor from a woman and had seen hirsuties disappear, it was not until 1904 that Bulloch and Sequeira[5] clearly outlined the relation of the adrenal gland to virilism. Apert,[6] in 1910, collected a considerable series of cases and confirmed the view that the obesity, amenorrhea and hirsutism were of adrenal origin. In 1921 Achard and Thiers[7] described their cases of "diabètes des femmes à barbe" in which the association of diabetes, amenorrhea and hirsutism was noted. This then, in brief, was the state of our knowledge in 1932 when Cushing published his excellent report. He sharply outlined a clinical picture consisting of a rapid, plethoric, painful obesity affecting primarily the face, neck and abdomen, but usually sparing the limbs, thus giving rise to an obesity of the buffalo type. The facial changes made the eyes appear small and slit-like, the so-called "pig eyes." There was acrocyanosis of the extremities with purplish lineae atrophicae on the thighs and the lower part of the protuberant abdomen. Hirsuties was marked and necessitated shaving by the women affected. There was a tendency toward polycythemia and hypertension, and glycosuria was a frequent finding, as was hypercholesterolemia. There was mus-

* Read October 30, 1939 at The New York Academy of Medicine in the Twelfth Graduate Fortnight.

cular weakness and osteoporosis which led to a cervicodorsal kyphosis with shortened stature. Occasionally, the osseous changes led to pathological fractures. Amenorrhea was present in the females and impotence in the males. In addition there was a marked susceptibility to infectious processes, particularly of the skin. Mental changes seemed to be an integral part of the syndrome, and fully developed psychoses were seen. Renal damage, including malignant nephrosclerosis, has been noted.[8]

Cushing attributed this clinical picture to the presence of a functioning basophilic adenoma of the anterior lobe of the pituitary gland and he reported clinical regression after x-ray treatment to the hypophysis.

In 1935 Oppenheimer and I[9] reported a patient we had observed in 1932 who presented all the features described by Cushing. At postmortem examination, the pituitary gland revealed no tumor even on serial section. There was, however, a large carcinoma of the adrenal cortex. At that time and again in 1937[10] we reviewed the literature and concluded that there were no clinical features by which we could differentiate cases of Cushing's syndrome due to an adrenal tumor from those due to a basophilic adenoma of the pituitary.

Our clinical material consists of seven patients who all presented typical c'inical features of Cushing's syndrome. These features need not be detailed again, but all of the patients were undoubted cases of the disease as you can see in the photographs (Figs. 1 to 6).

Of these seven patients, four were operated upon and the following were the operative findings:

One case of carcinoma of the adrenal cortex

Two cases of adenoma of the adrenal cortex

One case of normal adrenal glands (the only male case)

Two patients died on the medical wards and at postmortem examination there was found: in one, a carcinoma of the adrenal cortex; in the other, simple hyperplasia of the adrenal glands, combined weight 24.4 grams. We were unable to complete our studies of the seventh case. An eighth case due to an adrenal carcinoma has been seen since this report was prepared. Of the four patients operated upon, all died. We were unable to secure permission to examine the pituitary gland in the three patients who had adrenal new growths. The pituitary gland revealed no tumor on serial section in the fourth case; that is, the male with normal adrenal glands at operation and postmortem. One of the patients operated upon, the patient with an adrenal carcinoma, survived the operation

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 1: Author's case, Cushing's Syndrome, due to adrenal cortical carcinoma.
Fig. 2: Author's case, Cushing's Syndrome, due to adrenal cortical adenoma.
Fig. 3: Cushing's case, Cushing's Syndrome, due to basophilic adenoma of the pituitary.
Fig. 4: Turnbull's case, Cushing's Syndrome, due to thymic carcinoma with adrenal cortical hyperplasia.
Fig. 5: Wieth-Pedersen's case, Cushing's Syndrome, due to sarcoma (?) of the pituiary; adrenal cortical hyperplasia.
Fig. 6: Author's case, Cushing's Syndrome, no anatomic lesion in any of the endocrine glands.

for two months. In this period a remarkable improvement took place. The plethoric obesity of her face disappeared, the blood pressure returned to normal levels, the menses returned and the glucose tolerance improved. The restoration toward normal was striking, and there was no doubt that it was the result of the removal of the adrenal tumor.

Of the seven patients studied by us, four had tumors of the adrenal glands, two had no tumors either of the adrenal or pituitary glands, and the seventh could not be followed. No one of our three patients whose pituitary glands we could examine showed a basophilic adenoma.

Hirsutism and the Differentiation of the Various Types

The most striking single clinical feature in the symptom complex under discussion is the presence of hirsuties. This is particularly marked in the females who constitute a great majority of the cases so far reported.

From a pathologic-anatomic viewpoint there are five groups of lesions associated with hirsuties, namely:

1) Pineal tumors, usually teratomas
2) Ovarian tumors (arrhenoblastomas of Robert Meyer)
3) Thymic tumors
4) Adrenal cortical tumors
5) Basophilic tumors of the pituitary (Cushing)

There is an additional group of cases in which hirsuties is a prominent feature and at autopsy no anatomic evidence can be found in any of the endocrine glands to explain its presence. This "idiopathic group" has been known for a long time and in its minor forms may be seen daily in any obesity or endocrine clinic. These patients are characterized by their general well-being, the failure of their symptoms to progress, and the absence of any physical or laboratory findings to explain their complaints. When they present only hirsuties and obesity they are merely cosmetic problems and are left alone, but when they show progressive deterioration, loss of sexual power, hypertension, osteoporosis and other features of well-developed basophilism, they are very difficult problems in diagnosis and therapy. That even complete, typical cases of Cushing's syndrome may present no tumor formation in any of the endocrine glands is proved by two of the patients in our series and other cases in the literature.

The hirsutism of pineal lesions usually presents no diagnostic diffi-

culties with regard to pituitary basophilism. The cases are almost all examples of pubertas praecox in young boys. The typical obesity with striae is absent, hypertension is uncommon, and the signs of an intracranial lesion usually make the diagnosis fairly obvious.

The arrhenoblastomas of Robert Meyer present hirsuties as a leading symptom, but obesity and hypertension are not usually associated. These patients, as a rule, should present no problem, but if either obesity or hypertension, or both, should be associated with the hirsutism due to the ovarian growth, the differential diagnosis from pituitary basophilism might not be easy. This is especially true when it is recalled that the ovarian tumor may escape detection by physical examination.

The patients with thymic tumors who present hypertrichosis are particularly interesting. The three recorded examples presented practically all the features outlined by Cushing as occurring in pituitary basophilism. In fact, in one case the findings were so suggestive as to lead Cushing himself to predict that a basophilic adenoma would be found as the anatomic lesion. Serial sections of the pituitary revealed no tumor or basophile preponderance, but marked adrenal cortical hyperplasia was found in all three of these cases of thymic tumor. It is probable that the clinical features were a manifestation of the adrenal hyperplasia. The literature contains many examples, including our own, of patients who presented all the features of Cushing's syndrome clinically. At postmortem these showed normal pituitary glands so far as tumor formation is concerned but marked changes in the adrenal cortex consisting of cortical adenoma, cortical carcinoma or simple cortical hyperplasia.

To complete the pathological variations, typical cases of Cushing's syndrome have been reported where the only lesion found was the one predicted by Cushing, namely, a basophilic adenoma of the pituitary. This lesion has been present alone in several of Cushing's cases and in others reported in the literature. Pardee,[11] in a relatively recent review, is of the opinion that the basophilic adenoma is the basis for the syndrome. We cannot, however, agree that osteoporosis is of any value in the exclusion of cases of adrenal origin. We have seen marked generalized decalcification of bone with pathological fractures in cases due to proved adrenal tumors.

At this point I should like to show you photographs of seven patients who presented typical examples of Cushing's syndrome clinically. I

Fig. 7—Perirenal insufflation of air showing tumor of adrenal gland.

think you will agree that the patients present a remarkable similarity, yet each one had an entirely different lesion pathologically. There can be no doubt, that we are dealing with a clinical syndrome, not a pathological entity and yet there must be some underlying common denominator in all these varied lesions to result in such clinical similarity. We believe that denominator to be altered adrenal function (Figs. 1 to 6).

There have been several clinical and laboratory aids that seem to be of some use in studying these cases. First, Cahill and later, Mencher have been very successful in delineating the size of the adrenal glands and the presence or absence of an adrenal tumor by x-ray examination after the injection of air into the perirenal tissues. Figure 7 is the roentgenogram of one of our cases in which the tumor was demonstrated and later removed surgically (Fig. 7).

In 1934 Robert T. Frank[12] demonstrated the presence of greatly increased estrogenic activity of the urine in cases of Cushing's syndrome due to an adrenal cortical carcinoma. This finding has been confirmed for the group here reported. Interestingly enough, it was not present in the two cases of benign cortical adenoma studied.

In 1933 Broster and Vines[13] reported a specific staining reaction for the cells of the adrenal cortex in cases of virilism. They stated that the cortical cells stained a deep red when treated with the Ponceau-fuchsin stain, the so-called "fuchsinophilic reaction." Later studies have failed to substantiate the specificity of this reaction.

In 1935 Crooke[14] reported that the only constant pathological feature in all the cases of Cushing's syndrome that he could study was a peculiar hyalinization and vacuolization of the cytoplasm of the basophile cells of the pituitary gland with the disappearance of the normal granular structure of the cytoplasm. He found this change in Cushing's original cases, in the cases due to thymic tumors and in some cases due to adrenal tumor or hyperplasia. The change was present in the cells of the anterior lobe, and not in the cells of the basophile tumor itself in those cases in which a basophile adenoma was present. Crooke found this change in every case of basophilism which he could study and states that it is the anatomic basis for the syndrome. This hyalinization of the basophile cells was present in all three of our own cases which were studied. Gellerstedt[15] confirmed this finding and added that in his opinion "the basophile adenoma has no significance as an etiological factor in Cushing's syndrome." More recently Ecker[16] studied 721 pituitary glands from normal subjects and found the change described by Crooke in only 1.1 per cent. He also found the same alteration in 5.5 per cent of seventy-two basophilic adenomas from patients who did *not* present Cushing's syndrome. Ecker concludes: "It appears, therefore, unwarranted to consider hyalinization . . . as invariably associated with the state designated as pituitary basophilism." Nevertheless one is struck by the low incidence of the changes noted by Crooke in this large control series and the high incidence in basophilism. It seems to me that the changes described by Crooke are significant.

In 1939 Crooke and Callow[17] reported the excretion of large amounts of androgenic substances and the presence of trans-dehydro-androsterone in the urine of patients suffering from Cushing's syndrome due to malignant adrenal tumors. These androgens were not present in excess in similar clinical cases due to other lesions. They suggest that excessive androgen excretion, which can be approximated by a simple colorimetric test, indicates an adrenal tumor in cases of Cushing's syndrome. They were unable to confirm Frank's finding of increased estrogenic substances in their two cases.

Prognosis and Treatment: The condition is a serious one. Most of the patients survive only several months to several years, although Cushing himself described a patient alive after 22 years, and Rolleston quotes a patient of Maranon's alive after 17 years. Obviously, the prognosis varies with the pathologic basis of the syndrome and not too much can be expected in patients suffering from malignant disease of the adrenal, thymus or pituitary.

Cushing recommended radiotherapy to the pituitary gland and reported very striking results. Other observers have confirmed his observations, but this therapy frequently is unavailing. Because the pituitary tumors are usually very small, surgical approach is rarely indicated, although it has been attempted and radium has also been implanted directly into the hypophysis after surgical exposure.

It is in those cases of Cushing's syndrome due to an adrenal lesion that it is particularly important to make an early diagnosis, because it is in this group that brilliant surgical results have been achieved with complete restoration to normal. It is obvious that early recognition is particularly vital in malignant diseases if we are to expect favorable results. We are fortunate in possessing several direct leads enabling us to detect the adrenal cases and we wish to enumerate them now for emphasis:

1) Perirenal and periadrenal insufflation of air with x-ray photographs; pyelographic studies are an additional aid.
2) Biologic assay of urine for estrogens.
3) Biologic and chemical assay of urine for androgens.

In addition, this group is rare in men, occurs in women and is most frequent in female children.

All who have had surgical experience with these patients are aware of the very high operative mortality. We have attempted to reduce this by active treatment to combat surgical shock and adrenal failure, and have used large doses of adrenal cortical hormone postoperatively.

In closing this part of the discussion greatest credit should be given the contributions of Harvey Cushing to this subject. Even if "basophilism" in a strict sense is not the entire answer to the problem, we are all indebted to Cushing for his clear clinical delineation of the syndrome and for our renewed interest in it.

In the preceding discussion I have considered some tumors of the adrenal cortex which present endocrine disturbances as clinical features. Professor Young will present some other clinical features of hyper-

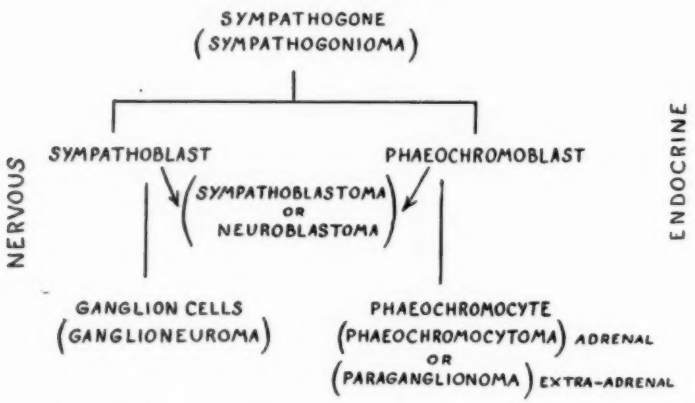

Chart I—Chart showing origins of adrenal medullary cells and tumors derived therefrom.

function of the adrenal cortex. There remain to be discussed those tumors which originate from the adrenal medulla. Chart I indicates the differentiation of the cells of the adrenal medulla and the tumors that may arise at the various stages of development. Of these tumors only those derived from the pheochromocytes have endocrine significance (Chart I).

The sympathogoniomata are a very malignant group of tumors that occur during intrauterine life or earliest infancy. They are usually bilateral and result in early death. They include many of the so-called retroperitoneal sarcomas and the round-cell sarcomas of infancy.

The neuroblastomas are tumors that usually occur in childhood and present themselves clinically as retroperitoneal malignant growths. In 1901 Pepper[18] reported one case and reviewed five others. In 1907 Hutchinson[19] reported ten cases of adrenal "sarcoma" in children with metastatic deposits in the skull and orbits. From a histological point of view the tumors described by Pepper and Hutchinson are identical, but there has persisted a clinical differentiation. The Pepper type is characterized by the preponderance of abdominal signs, a large liver, ascites and cachexia. The Hutchinson type presents tumors in the skull, especially about the orbits, with proptosis and ecchymosis of the eyelids, and may resemble chloroma or infantile scurvy.

It has been suggested that the Pepper, or abdominal type, results

from a tumor of the right adrenal gland because of its intimate vascular and lymphatic connections with the liver, while the Hutchinson or osseous form of the tumor arises from a primary lesion of the left adrenal gland as a result of lymphatic drainage to the left intercostal vessels and through the deep cervical chain to the base of the skull. It is doubtful whether this schematic concept is adequate. These tumors are not associated with the sexual changes seen in cortical tumors and are without endocrine significance.

New growths derived from the mature pheochromocytes may occur in any location where pheochrome tissue exists. They have been reported as arising in the carotid body, the retroperitoneal tissues, along the abdominal aorta and its branches, the organ of Zuckerkandl, and in the sacrococcygeal region as well as in the adrenal medulla itself. The general clinical features are similar no matter where the tumor originates, and are due to the secretory activity of the growth. Large amounts of adrenalin have been isolated from such tumors. Belt and Powell[20] estimated 20 grams of adrenalin to be present in a growth weighing 1000 grams.

The patients are usually adults although the tumor has been reported as early as the second year of life, and as late as the eightieth. The growth is rarely bilateral, and may vary in size from several millimeters to 12.5 cm. in diameter.

The tumors are well encapsulated and often surrounded by a shell of normal adrenal medulla and cortex. They are prone to hemorrhage and necrosis with cystic changes. Microscopically, the tumors consist of nests or cords of polyhedral cells separated by their connective tissue stroma rich in capillaries. The predominating cellular element is a polyhedral cell with abundant finely granular cytoplasm, and a large nucleus containing a chromatic network. The affinity for the chrome stain is variable, some cells staining deeply and others lightly or not at all. Hyaline inclusions are present.

The characteristic clinical feature presented by these tumors is the occurrence of paroxysmal crises which may occur spontaneously or may be induced by emotion, exposure to cold, physical strain, manipulation of the tumor, or any of the pharmacological procedures known to cause adrenalin secretion. These crises resemble the symptoms produced by a large dose of adrenalin, namely: anxiety, pallor, tremor, sweating, nausea, vomiting, headache, cardiac palpitation, tachycardia,

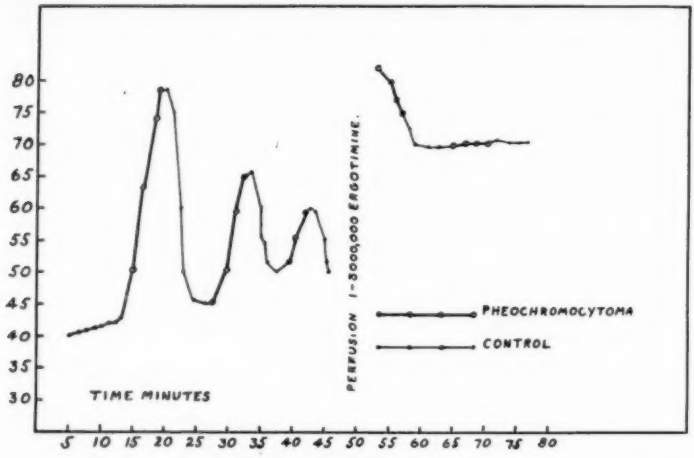

Chart II—Illustrating pressor effect of patient's plasma when perfused through denervated rabbit's ear and the reversal effect of ergotamine. (From Beer, King and Prinzmetal)

a feeling of constriction in the chest, dyspnea, hyperglycemia, glycosuria and a sudden marked increase in blood pressure, particularly systolic. As a rule, the relative rise in the systolic blood pressure exceeds the rise in diastolic pressure but diastolic pressures of 240 mm. of mercury have been reported. The paroxysms may be rare or may occur as frequently as every 30 minutes. In the early phases the blood pressure may be normal between attacks, but as the disease progresses, permanently high blood pressure with all of its cardiovascular concomitants is encountered. Death may occur in shock or pulmonary edema during a paroxysm, and sudden death has been reported after such trivial procedures as a tooth extraction, anesthesia or a minor operation.

Clinically the syndrome is frequently confused with exophthalmic goiter, and in several cases thyroidectomy has been performed. The association with thyroid adenoma and thyroid carcinoma has been recorded.

The final evidence for the hormonal nature of the symptoms, the demonstration of a hyper-adrenalinemia was long delayed. Earlier attempts are recorded, but I think that the first demonstration of the presence of an excess of adrenalin in the circulation during a paroxysm was made by Beer, King and Prinzmetal.[21] In 1937 they observed a

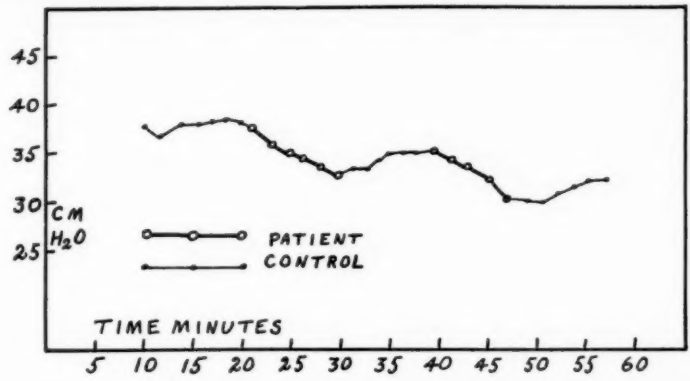

Chart III—Illustrating absence of pressor effect of patient's plasma following operative removal of tumor. (From Beer, King and Prinzmetal)

patient with a pheochromocytoma in whom crises could be induced by exercise. I show you two of their charts. The first shows the vasoconstrictor properties of the plasma and the disappearance of these properties after ergotamine. This is strong presumptive evidence of the presence of circulating adrenalin or at least an adrenalin-like substance. The second shows the absence of vasoconstrictor properties in the serum after the tumor had been removed (Charts II, III).

There have been presented this evening two interesting and important clinical states. One of these, due to a tumor of the pheochrome tissues, is quite clear-cut in its pathogenesis, clinical features and treatment. The other, Cushing's syndrome, is still in the process of being moulded into its final shape. Time will decide whether it is really a pituitary, adrenal or polyglandular syndrome. It is, at least, an interesting one.

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SURGICAL CONSIDERATIONS IN THE TREATMENT OF CHRONIC LYMPHEDEMA AND OF VARICOSE VEINS*

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SURGICAL procedures should be based on physiological and clinical understandings of the problems, and elucidation of these problems by such authorities as we have heard tonight, makes one realize how ineffectually we have been forced to grope surgically without adequate preparatory knowledge. Surgery's history is one of trial and error, and with such careful physiopathological research to guide us, our responsibility in the operative field of the future will be greater.

The lymphatic system is one of great surgical importance, because our triumvirate of tissue response, localization and absorption from infection are dependent upon its proper function, while our concept of surgery in malignancy rests on *en bloc* excision of the tumor and its primary extent to neighboring lymphatics. My discussion of the lymphatic system will be confined to that group which we consider amenable to modifications of the original Kondoleon principle, namely, the elephantiasis cases. Many of these patients with lymphedema, from an etiological standpoint, are not classifiable in the light of our present knowledge. In an effort to clarify them, we have prepared a surgical classification based on whether or not they might be expected to respond to surgical intervention.

SURGICAL CLASSIFICATIONS OF LYMPHEDEMA

I. Amenable to Surgical Treatment
   1. Modified Kondoleon Procedure (as presented)
      a. Idiopathic
         1. Præcox
         2. Congenital or familial (Milroys)

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b. Acquired
   1. Trauma (accidental or surgical)
   2. Filariasis Bancrofti
   3. Occasionally group secondary to venous pathology

2. Local Surgical Intervention
   a. Pressure, growth, etc.
   b. Traumatic or operative scars
   c. Most venous obstructions
   d. Local inflammation
   e. X-ray, radium and other burns
   f. Congenital lymph collections (cystic hygroma, etc.)

II. Not Recommended for Surgical Treatment
   1. Milk idiopathic lymphedema
   2. Fungus infections
   3. Malignancies with invasion
   4. Allergic or systemic lymphedemas.

In a study of the last twenty-four patients diagnosed as having advanced lymphedema at the Vascular Clinic in New York Post-Graduate Hospital, eight have been the so-called simplex or præcox form, eight have followed chronic phlebitis—for the most part, after operation—five have been secondarily due to severe varicose venous pathology, two have been familial, or in the true Milroys group, one has been of filarial origin and two have followed infection—one after lymphangitis and one after epidermophytosis. During the past year eleven patients with occlusion of the lymphatic channels have registered. Two were post-infectional; one, post-traumatic; two, postoperative; and six were of the idiopathic type. For the past three years selected patients from this last group have been subjected to a modification of the original Kondoleon procedure and this modification will be described in detail.

The lymphatic system, being a separate and complete circulatory system of itself, resembles the venous system and picks up such tissue products as the venous system does not remove. In lymphedema, an occlusion occurs in the lymphatic vessels, which may be caused by pressure, inflammation or thrombosis. Fibrosis soon follows and the drainage of these lymphatic vessels is permanently closed, possibly accelerated by the increased protein content, which Drinker, Field and

Homans found to reach a height of 4 per cent. Lymph then accumulates in the tissue spaces, with no normal method of escape. With elevation of the part, it passes through the tissue spaces to the abdomen and is drained. With dependency, it again collects and with increasing distension the size of the part increases.

In mild cases of lymphedema, mere support is sufficient; the wearing of a rubber stocking and elevation of the leg for part of the day, with a restricted activity, permits these patients to continue quite satisfactorily. In certain patients, mecholyl by iontophoresis has relieved mild lymphedema and Irving Wright, of the Vascular Clinic, has a followed series of these patients. In others, however, supportive measures are entirely inadequate and in general the results have not been too encouraging. In progressive cases the part becomes so large that it is unwieldy and disfiguring, and with periodic febrile reaction, many of these individuals become economic liabilities. Some present themselves requesting amputation.

While the early conception of skin lymphatic drainage through muscles as suggested by Handley and Kondoleon is partly erroneous, and some of the beneficial results depend on excision of large sections of lymph accumulations in subcutaneous tissues, it appears that after the operation some of the lymph may be eliminated through the muscles. If this were not true, the local excisions of Dieffenbach and Mikulicz would have been more successful. Recent biopsies on our patients six and eighteen months after operation showed a normal histological arrangement of the fat cells and no lymph collections. If the therapeutic effect depended on local excision only, some lymph collections should be present in one and a half years.

Regardless of the manner in which the surgical removal of the subcutaneous tissue and fascia acts physiologically, it is a means of affording relief in a high percentage of patients. Preoperative and postoperative measurements in five extremities, which we have carefully watched for from six months to two years, have shown and maintained a reduction in the circumference of the leg from a minimum of seven inches in one patient, to a maximum of twenty-one and one-eighth inches in our most advanced case. All of these patients have had a one stage procedure, which can be briefly outlined as follows:

The patient is hospitalized, with the leg elevated, for two weeks, during which time diuretics are administered. The frequently accom-

panying fungus infection is cleared and sulfanilamide is given. This drug has been used somewhat empirically. Drinker and Fields showed in their work in experimental elephantiasis in dogs, that just as the febrile reaction occurs, there are streptococci present in the lymph and it is to eliminate these organisms that the sulfanilamide is given.*

We would emphasize the careful selection of the patient, the preoperative preparation, spinal anesthesia, measuring of the size of the leg, the undermining of at least three-fourths of the circumference, care at the joint, the use of alloy steel wire to reduce reaction and blood transfusion. By being sufficiently radical we have been able thus far to eliminate a second stage operation on the medial side of the leg. In only one instance have we had any slough and that was over the dorsum of the foot, where we tried considerable undermining. In this patient, we were operating on a recurrent lymphedema and the previous scars were a factor. Incidentally, the deep fascia had entirely regrown since a previous, much less radical operation at another institution five years before.

Surgical Treatment of Varicose Veins

While surgical eradication of Venous Pathology is at present much more advanced than that of the lymphatic system, we must admit to an even longer misunderstanding of the physiological problems on which our operations must be based. The consideration of all of the ramifications of the venous system, of course, is impossible, so I will confine my discussion to that of the varicose vein problem. The pendulum of conservative or radical therapy has swung back and forth somewhat more rapidly in the treatment of varicose veins than in other problems. Surgical history illustrates again that there is little new that one can do,

* A short motion picture was presented demonstrating the operation. This detailed a surgical technique consisting of an incision starting over the greater trochanter on the lateral aspect of the leg and continuing to the external malleolus, with an elliptical excision of skin sufficient to make the remaining circumference equal the unaffected leg. This incision was brought together at the knee to prevent joint constriction. A dissection of the skin flaps was then made until 75 per cent of the circumference of the skin of the leg had been raised from the fat layer. No transverse incision was employed. The incision was then continued through the fat and deep fascia layers and the skin, superficial and deep fascia were removed en mass, permitting the undermined skin to fall on the denuded muscle. After hemostasis was secured, the skin was closed with interrupted #32 and #36 alloy steel wire without drainage. Blood transfusion was performed and the limb was encased in supporting bandages. The patient was shown immediately and three months after the operation. Other patients were also presented by the motion picture, both before and after the operation.

except to better apply the understanding we have of physiological and pathological processes. Hippocrates ligated the saphenous vein and injections for varicose veins were performed the same year the syringe was invented. Our only improvement is in asepsis, surgical technique and the proper location of the ligation points.

To understand the varicose vein problem, the anatomy and physiology of the venous return from the leg must be briefly recalled. The venous return depends on a deep femoral and a superficial greater and lesser saphenous system. These deep veins are well supported and protected by muscle and adequately valved, while the saphenous veins are subcutaneous, subject to trauma and without muscle protection or support. The great saphenous vein, the one involved most commonly in varicose veins, drains the medial aspect of the leg and empties into the femoral vein at the fossa ovale. Reflux blood from the femoral vein normally is prevented from entering the saphenous vein by the saphenous-femoral valve and inadequacy of this valve permits femoral vein blood to flow reversely into the saphenous vein, with back pressure, further valve incompetence and varicose veins. The area on the medial aspect of the leg is inadequately drained, constantly bathed in stagnant, deoxygenated blood and the result is edema, discoloration, dermatitis and frequently ulceration. The two venous systems intercommunicate at other points and if the valves fail in these communicating branches, there will be reflux blood at these points also, the so-called "blow-out points." The lesser saphenous vein, draining the posterior aspect of the leg, empties into the popliteal vein. It may be involved in the process.

After a thorough survey of the patient has been completed, and a study of the arterial supply made, our problem with these patients is then to determine:

1. If the deep veins are open and adequate. This can be done simply by a modification of the Perthes test.
2. If the saphenous-femoral valve is incompetent; the Trendelenburg test shows this satisfactorily.
3. Incompetence of the valves of the communicating branches must be demonstrated and a very simple test, which we have devised in the Vascular Clinic has proven satisfactory to us. This is done by elevating the leg to empty the veins, applying a tourniquet below the fossa ovale to prevent saphenous-femoral reflux, and applying an Ace bandage from the toes to the tourniquet. With the patient

standing, the Ace bandage is removed from above down and any "blow-out," as it appears, is marked and measured from the lower tip of the patella.

4. Incompetency of the lesser saphenous must be recorded.

We now have completed the third year of a five year study, using the technique* outlined and our results, while too early to be conclusive, are very encouraging. There have been no deaths and no occurrence of anaphylactic shock. In four instances there have been allergic symptoms, manifested by febrile reaction, urticaria and local redness. In three patients there have been local sloughs, due we believe, to technical failure to apply pressure at an area of redness, indicating sclerosing solution collection. The catheter has been introduced on an average of 37.4 centimeters in the last one hundred cases and 26.2 cc. has been the average amount of injection. Of the patients who have been followed for over one and one-half years, we have had fifty-one entirely satisfactory, two partially satisfactory and two unsatisfactory.

The two partially satisfactory patients have been ones in which there was a plexus of branches at the fossa ovale requiring ligation only and

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*SYNOPSIS OF MOTION PICTURE PRESENTED TO ILLUSTRATE THE DESCRIBED TECHNIQUE

After infiltration with local anesthesia at the fossa ovale, the saphenous vein, together with its branches, was dissected free. After ligating and dividing the branches, the saphenous vein was resected at its femoral junction, the proximal end being transfixed and ligated. Through the open, distal end a ureteral type catheter was inserted for a distance of 50 cm. and a sclerosing solution (3½ per cent sodium ricinoleate) was injected, as the catheter was withdrawn.

The advantage of the catheter method was illustrated by sections of the veins of experimental animals which showed that the sclerotic effect from any injection solution is localized and to sclerose a large vein the solution must be uniformly and segmentally distributed.

The distal end was then resected for two inches and transfixed and ligated. The wound was closed without drainage. A secondary incompetent communicating branch or "blow-out" just below the knee was resected and ligated. The patient was then made to walk around the operating room and a supporting bandage was applied from the toes to the knee. Accumulations of sclerosing solution were prevented by pressure pads. As much as 10 to 50 cc. of the solution was the amount advocated for sclerosis.

While the amount of solution mentioned may sound radical to some, the reaction is so spaced throughout the vein course that local deleterious effects are unusual. A suggestion that the solution might enter the deep femoral system and cause sclerosis is more theoretical than actual. We have seen no evidence that this occurs in more than one hundred and fifty injections performed with this technique. We know that sclerosing solutions in the form of 50 per cent glucose, are injected daily in competent veins without ill effect and the use of the moving catheter restricts the amount of the solution that would run into the deep vein at any one point.

later injection at the clinic. We have not had as satisfactory results when the injection is performed secondarily, due we believe, to inadequate saphenous sclerosis in the thigh, where local injections are often difficult. The two unsatisfactory patients both had chronic phlebitis and probably incompetent communicating branches, masked by the chronic edema. The postphlebitic group definitely are more difficult to treat. The sloughs were approximately the size of a silver quarter. These slowly granulated, requiring about six to eight weeks. The only slough that has occurred since the postoperative routine inspection was established, was at the Welfare Hospital in an elderly, bed-ridden individual.

Improvement of Arterial Circulation By Saphenous Vein Sclerosis

Restricted arterial circulation always has been a contraindication to varicose vein injection and Homans has stated that a thrombosis in a vein may cause an arterial spasm, which may result in gangrene. We had noticed a decrease in the oscillometric readings in all of our varicose vein patients after ligation and retrograde sclerosis, which indicated that less arterial pressure was necessary for circulation after the inadequate veins were eliminated. In studying the physiology of the capillary system, it seemed to us that some of these patients with deficient arterial supply would have their arterial circulation improved if the peripheral resistance could be reduced. The capillary system is part of the peripheral resistance and is a closed system—the blood actually coming in contact with tissue cells in only two organs, the liver and the spleen. Taking the data of Landis as a criterion for discussion, the pressure in the arterial end of the capillary loop is approximately 32 mm. mercury. The osmotic pressure in this area is twenty-five, thus giving an outward driving force at the arterial end of plus seven. At the venous end of the capillary the intracapillary, or outward force pressure, has fallen to twelve, which is below that of the osmotic pressure, which is slightly increased, due to concentration, thus normally permitting an equal absorption from the tissue spaces at the venous end. In the presence of varicose veins, with obstructed venous outflow, the pressure at the venous end of the capillary increases and may rise higher than that of the arterial end. Beecher lately has shown that there is an increase in the positive pressure in the saphenous vein in varicose veins which averages 50 cm. of water in excess of colloidal pressure. Thus in varicose veins, the normal re-

absorption of tissue fluid at the venous end is impossible and tissue fluid must be carried off by the lymphatic system, if at all. An increased capillary and peripheral resistance follows, thus making the blood supply through arteries already damaged, more difficult. Elimination of varicose veins, if safely accomplished, should be expected to improve the arterial circulation. In a group of patients suffering from advanced occlusive vascular disease—six with advanced arteriosclerosis and three with thromboangiitis obliterans—accompanying varicose veins have been eliminated by the procedure already mentioned and clinically all but one patient has been improved. Claudication has decreased, oscillometric readings have been lowered, thus indicating the necessity of less artery pressure. In one instance, a trophic ulcer quite promptly has healed. In the one unsatisfactory result, a major amputation, unrelated to this procedure, was necessary one year later. Further investigation along this line is being done at this time. Care is necessary to prevent accompanying arterial spasm by using a small amount of solution, closely watching the postoperative course and at times, using antispasmodics.

The history of varicose vein therapy has shown us that it is difficult to say that any specific procedure is satisfactory until many years of observation have passed. We do think, however, that our present line of attack is physiologically and anatomically more sound and we hope that our subsequent follow-ups will bear this out.

MECHANISM OF ALLERGY*

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THE TERM allergy is applied to a variety of conditions based on different forms of specific hypersensitiveness. In the present communication, discussion will be limited to the mechanism operative in that group of allergic diseases known as the atopic illnesses. In this category, hay fever and asthma are the outstanding examples, although certain forms of infantile eczema, urticaria, angioneurotic edema, and other food and drug sensitivities may also be included.

The term atopy is applied to the above mentioned clinical conditions on the principle that they are all hereditary in nature. The hereditary factor manifests itself in its influence upon the number of offspring affected and upon the age of onset of the illness. To a lesser degree, the particular form of atopy which develops, as well as the nature of the sensitivity, is affected by the hereditary influence.

The mechanism of anaphylactic shock, which, by definition, involves the participation of precipitin anchored in a shock tissue of smooth muscle, has not been found operative in atopic reactions.

The typical atopic reaction is ordinarily described as that resulting from the union in certain predisposed tissue cells or shock tissues, of an excitant or allergen with a peculiar antibody known as the atopic reagin. This antigen-antibody reaction occurring on or within the cells, according to the theory of Lewis and Dale, results in the liberation of histamine or a substance of a similar nature which produces an increased vascular permeability. The resulting edema is the most important factor in the production of clinical atopic symptoms.

The allergen-reagin reaction seems not to be the sole means by which the atopic shock tissues may be stimulated. The same result may be effected by mechanisms in which neither reagins nor any other antibodies can be demonstrated. There is reason to believe that, under cer-

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tain circumstances, the shock tissue may even be stimulated non-specifically.

The atopic reagin is the peculiar human antibody which mediates the positive cutaneous reactions elicited by skin tests with various allergens in the diagnosis of atopic illnesses. Although primarily a circulating antibody, it manifests a definite affinity for various tissues. Its affinity for the skin is demonstrated by the ease with which any normal human skin can be passively sensitized by an intracutaneous injection of a reagin-bearing serum. In a series of studies in mucous membrane hypersensitiveness, Sherman and Gray and their co-workers have shown that the human ophthalmic, nasal and intestinal mucous membranes can be sensitized as easily as the skin by intramucosal injections of reaginic sera. In fact, when skin and mucous membrane were locally sensitized with injections of the same serum and the related antigen was administered either orally or parenterally, the reaction at the site in the mucous membrane usually preceded that at the cutaneous site by several minutes. Evidence of the affinity of the atopic reagin for placental tissue is found in the fact that Bell and Eriksson and all subsequent investigators have never found maternal atopic reagins in the fetal circulation, although other maternal antibodies regularly pass through the placenta. Even when he actively induced sensitization during pregnancy with the antigen of Ascaris lumbricoides, Zohn could not detect any of the maternal atopic reagins for this antigen in the cord blood at birth. It is undoubtedly this affinity of the reagins for the placental tissue which renders the passive intrauterine sensitization of the human fetus highly improbable.

The affinity of the atopic reagin for animal tissues had not been satisfactorily demonstrated until the recent experiments of Caulfeild and Straus definitely established the possibility of sensitizing the skin of the Rhesus monkey with these antibodies. Further studies by Straus and his co-workers demonstrated the ability of the human atopic reagin to sensitize the stomach, intestines, gall bladder and spleen of the Rhesus monkey. The peritoneum could likewise be passively sensitized, giving experimental basis for the belief that serous surfaces in humans may also participate in atopic reactions. Attempts at passive sensitization with the atopic reagin in laboratory animals other than the monkey have thus far proved unsatisfactory.

The question as to whether atopic reagins can be produced by

experimental animals is not yet answered. However, the results of recent experiments on guinea pigs and rabbits by Sherman, Stull and Hampton, by Caulfeild and by Eagle and their co-workers support the earliest contentions of Cooke and Spain that certain immune rabbit sera can passively sensitize some human skins. Because of the irregularity with which such sensitization is accomplished with each serum, and because of the atypical nature of the reaction resulting from testing the sensitized sites, it is not yet clear whether these unusual skin-sensitizing antibodies are the same as the atopic reagins. This question needs further investigation.

In contrast to the relatively strong attraction existing between the precipitin and its antigen in anaphylactic sensitivity, the reagin and its specifically related allergen are only loosely bound to each other. The affinity of the reagins for the tissue cells is much stronger than that for its antigen. Hence, reagins may sensitize the human skin cells even in the presence of antigen.

A mistaken impression commonly held is that the atopic reagin is the sole criterion for the diagnosis of atopy. There are certain types of antigens, however, such as Ascaris lumbricoides, Trichinella spiralis, horse serum, insulin, and liver extract which stimulate reagin production equally well in non-atopic and atopic individuals. On the other hand, there are some forms of atopy in which reagins are absent and in which even the involvement of an immunologic mechanism may be questioned. It is obvious, therefore, that the heredity of a predisposed shock tissue is much more fundamental in the concept of atopy than is an immunologic mechanism involving a hypersensitiveness.

Unlike laboratory animals in anaphylaxis, man has no characteristic atopic shock organ. One is even at a loss to designate the shock tissue in which the atopic reaction takes place, although many observers consider the reaction primarily a vascular one. However, the smooth muscle, which is acknowledged to be the primary shock tissue in anaphylaxis, has now been ruled out as a possible atopic shock tissue by most investigators. Failure to sensitize the guinea pig smooth muscle with human reagins was consistently obtained by Coca and Grove and by subsequent workers, while recent experiments have yielded evidence in the same direction which is even more convincing. Although the skin and mucous membranes of the Rhesus monkey can be easily sensitized with small amounts of human reaginic sera, Albert, using the Dale technique,

could demonstrate no fixation of reagins in the smooth muscle of the monkey's intestinal strip even though excessive amounts of potent reaginic sera were used for sensitization. Using a human uterine muscle segment obtained from a patient with a positive cutaneous reaction and with circulating reagins for horse serum, Tuft also failed to elicit specific contractions with the Dale technique. Approaching the problem from a different angle, Feldman and Sherman, by means of the slit lamp, studied the responses of naturally and passively sensitized human conjunctivae to excitation with the specifically offending allergens. No evidence of vascular contraction was detected at any time during the allergic reactions. There exists, therefore, no experimental justification for the assertion frequently made by the clinician that, in bronchial asthma and in gastrointestinal allergy, the smooth muscle is the primary seat of the allergic reaction.

Evidence recently obtained also tends to exclude the epithelial lining of the mucous membranes as the seat of the allergic reaction. Of interest in this connection have been Grayzel's observations in microscopic studies of the allergic reactions in the organs of the Rhesus monkey passively sensitized with human reaginic sera. In the gall bladder and intestines, the blood vessels and the connective tissue of the lamina propria and submucosa seemed to be most affected while the epithelial cells and muscle cells appeared least involved. Marked edema of the loose tissues, engorgement of the vessels, and infiltration of the connective tissues with cells, frequently perivascular in distribution, were findings common to all specimens.

There is additional experimental evidence to indicate that the seat of the atopic reaction is not in the epithelial layers of the sensitive mucosa. Sherman and Kaplan reported that topical applications of the specific excitant to the passively sensitized nasal mucous membrane in humans was far less effective in inducing an allergic reaction than an intramucosal or parenteral injection. Similarly, Gray found that, in the passively sensitized human rectal mucous membrane, the local application of the specific excitant to the sensitized site did not, as a rule, produce a maximal allergic response. The reaction seemed to reach its height only after the excitant had been absorbed into the circulation, the occurrence of the latter being marked by the spontaneous lighting up of a cutaneous site sensitized with the same reaginic serum. Hence, the passively sensitized mucous membrane sites seemed to receive a weaker excitation from

local contact with the antigen than from its absorption, through the mucous membrane, into the circulation and its contact with the shock tissues from within. The fact that this can occur renders it unlikely that the epithelial cells which line mucous membranes are the ones most involved in the atopic mechanism.

The hypothesis that the increased vascular permeability in the allergic reaction results from the liberation of histamine or a histamine-like substance does not appear to be entirely adequate. Abrahamson by iontophoretic methods could not detect the presence of histamine in allergic wheals. Bowman, in clinical studies, showed that a reaginic reaction in the naturally sensitive skin increases the capillary permeability at that site upon subsequent stimulation, while a histamine reaction produces the opposite effect. The allergist finds confirmation of an increased vascular permeability following atopic reactions in the fact that, after a constitutional reaction resulting from pollen therapy, the patient's tolerance to dosage is definitely diminished. Despite these weaknesses in the histamine hypothesis, a more satisfactory theory is not yet available.

There are still many who believe that sensitization to foods and inhalants is an accidental phenomenon based on the degree and interval of exposure to these allergens. That adequate antigenic stimulation is necessary for the development of hypersensitiveness is generally agreed, as is also the fact that the absorption of traces of ingested and inhaled antigen into the circulation in an unaltered form is a normal and physiologic phenomenon which facilitates sensitization to all of these allergens. The recent studies of Harten and Bowman, however, have yielded convincing evidence that, in atopic individuals, the hereditary predisposition to become sensitive to certain antigenic groups plays an important role in the sensitivities which are developed. It was found that of 500 patients with frank pollinosis residing in this city, all of them, with only six exceptions, showed positive cutaneous reactions of varying degree to representatives of all of four groups of ubiquitous pollen, namely, timothy, ragweed, plantain and trees. For the latter test a mixture of six common tree pollens was used. These positive reactions were specific, as they were transferable to normal skins in more than 97 per cent of trials. In 100 atopic cases with no frank hay fever symptoms, uniformly negative reactions to all of the four pollen groups occurred in 37 per cent and uniformly positive ones in 55 per cent. In 8 per cent

there was an absence of uniformity. Two sera obtained from hay fever cases in Hawaii, where the pollinating flora is different from ours, showed a lack of uniformity when tested for the presence of reagins for the aforementioned four pollen groups. Since there is no evidence of a common antigen in these pollens, the findings point strongly to a predisposition in pollinosis cases to sensitization to the pollen antigens. The preponderant uniformity in the co-existence or absence of such sensitivities excludes degree and interval of exposure as significant factors in their development. The conclusion seems justified that the element of accidental or unusual exposure to common allergens is of much less importance in inducing atopic hypersensitiveness to these substances than is generally assumed to be the case.

ALLERGY IN CHILDHOOD*

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THE earliest common clinical manifestation of allergy is eczema. The eczema problem is made difficult by the fact that under this heading are grouped several dermatoses which are unrelated etiologically, but which may be similar in appearance. However, it is probably true that at least 75 per cent of eczematous infants are allergic.

The first allergen to which most of them become hypersensitive is egg white, although they have never eaten it. Whether the sensitization is hereditary, congenital, or by transmission of antigen through the breast milk, need not concern us here—the important practical fact is that the baby is either born sensitized, or is sensitized in the first few weeks of life. Although egg white is the most common allergen concerned in hypersensitivity when the baby has never eaten the food in question, the same thing may occasionally happen with other allergens, notably fish and nuts. This congenital or possibly hereditary sensitivity is usually of high degree: the baby is likely to be made violently ill if he eats even the smallest amount of his allergen. Although such sensitivities often occur in infants with eczema, they presumably are not directly concerned in its causation, for the sensitization is usually of such quality that the infant can take none of the food. Those sensitizations which cause eczema are milder, and to allergens to which there is continuous or frequent exposure without violent symptoms.

The most important allergen with which the young infant, already usually sensitized to egg white, next comes in contact, is cow's milk. He takes the same amount of milk protein regularly day after day and with modern methods of feeding in excessive quantities; as a rule over twice as much as if he were breast fed. He has been taking also orange juice, and soon begins with cereals and various vegetables. He may become sensitized to any of them. Many normal infants will for a short time give positive intracutaneous skin tests and have antibodies

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in the blood after the introduction of a new food into the diet. The eczematous infant prolongs and exaggerates this normal immunologic response, and while he is doing so, he has eczema. Although it is by no means true that all such infants are sensitized to milk, and while sometimes other foods may be of more moment, it has seemed to me that this is by far the most important allergen in early life, and the one to which attention should be chiefly directed in any study of the immunology of infantile eczema. In a series of 153 infants under one year of age, with all sorts of eczema, allergic or non-allergic, 17 per cent gave positive scratch tests to milk. In another series of sixty-four, all with negative scratch tests, 56 per cent gave positive intracutaneous tests. Normal infants who have been taking milk for a considerable time, as did all these infants, do not react to it, so such positive tests are abnormal. Their etiologic significance, however, is quite another matter, and not all positive intracutaneous tests are etiologic. However, if the scratch test to milk is positive, it has been my experience that the eczema is almost always due to milk. The same holds true for wheat and other foods.

Of the two chief milk proteins, casein and lactalbumin, lactalbumin is by far of most consequence. It has been said that casein was of no significance as an allergen. I think, however, that Dr. Pratt and I have been able to show, in work soon to be published, that sensitivity to casein is not uncommon in infantile eczema.

Sensitization to the environmental allergens is not so frequent in early life as later, but can by no means be ignored. Many eczematous infants are at an early age sensitized to house dust and feathers, two allergens to which they are constantly exposed. There is no reason for believing that these are not of etiologic significance, but it is hard to prove that they are. Sensitization to other environmental allergens is only occasional during the first year.

Infantile eczema usually develops on an allergic soil, and what has been learned about allergy in the last few years has given at least a rudimentary understanding of eczema. Dietetic treatment, however, has been wrongly used so frequently in eczemas that have nothing to do with the diet, that dermatologists in particular, and sometimes rightly, have become skeptical of any but local treatment. However, there can be no doubt that the present conception of immunologic treatment, that is, removal from the diet or environment of those aller-

gens to which hypersensitivity exists, represents a real advance, even though there are many difficulties and inconsistencies attached to this conception, and even though it does not entirely explain eczema.

It is not difficult to plan a diet for an allergic infant, with the exception of milk: hence I shall not discuss the other foods. The common practice of trying this milk and that, dried milks, patent foods, and various sugars, does no good.

There are three methods of handling the milk situation that may do some good:

1) The use of heated milk (usually evaporated)
2) Goat's milk
3) A milk free food

It has been my experience that in eczema heated milk is not often of value. The reason for this is probably that while the antigenicity of lactalbumin is changed somewhat by heating, it may not be changed enough, and that casein is not changed at all, so that if casein sensitivity is present, there is no reason why heating should do good. I have many times seen eczema due to milk sensitivity cured with a milk-free food, only to recur when evaporated milk was resumed, and cured again when it was omitted. In spite of these objections it is probably the best form of milk if any cow's milk is used.

With goat's milk results may be occasionally very satisfactory; more often no better than with cow's milk. Goat casein is immunologically the same as cow casein, and in thirty infants who gave positive skin tests to cow casein, also tested with goat casein, there were identical reactions to both in every case. It has been commonly said that goat and cow lactalbumin were species specific, but there has been no original work done upon which to base this assumption, except that by Versell in 1915, who found only that goat and cow lactalbumin were more species specific than goat and cow casein, but by no means entirely so. We tested forty-four eczematous infants who gave positive reactions to cow lactalbumin with goat lactalbumin of the same strength. There were ten entirely negative reactions to goat lactalbumin, nine doubtful reactions, much smaller than those to cow lactalbumin, and twenty-five identical positive reactions to both. It is well known that some proteins contain two or possibly more antigenic determinants, one species specific, and one common to the protein in question and to other closely related proteins as well, and that an individual may

become sensitized to only one or to both of these determinants. Such seems to be the case with eczematous infants.

So milk sensitivity in eczema is in reality more complicated than appears on the surface. Some infants are sensitized only to the species specific factor of cow lactalbumin, others to the factor common to both cow and goat lactalbumin, and in either of these two groups there may be sensitization to casein as well. In still a third, but much smaller group, there may be sensitization to casein alone. It is probably due to this situation that goat's milk is not more often effective in dietetic treatment.

The ideal diet for any milk sensitive infant, provided he can digest it and thrive on it, is a food which contains no milk. With this in mind, we developed some ten years ago such a food, the basis of which is soy bean flour, and since then several other similar preparations have appeared. It has been our experience that better results are obtained with these foods than with any form of milk. If the eczema is caused by milk, it will be cured with a milk free diet; if it is not, such a diet is no better than milk. However, the soy bean foods have the disadvantage that they sometimes cause loose bowel movements and irritated buttocks. This is probably due to some property of the soy bean flour. We have found, however, that by boiling in a double boiler for three-quarters of an hour, this property is considerably lessened. We have had opportunity to feed many milk sensitive eczematous infants on such a milk-free diet, and consider it a valuable adjunct.

However, it is surely not wise to use a milk-free food as a routine. If the eczema is mild, whether or not skin tests to milk are positive, it can be very well controlled with local treatment, and it is unwise to make such a radical change in feeding. If skin tests have not been done, the use of such a diet is not the careful practice of medicine: the eczema may not be due to milk. In very young or in poorly nourished infants the risk of a digestive upset is too great. In erythroderma, where there is diffuse redness and scaling all over the body, blue feet, and a general glandular enlargement, a milk-free diet is not likely to do much good, in spite of the fact that these babies are strongly allergic and often give positive tests to milk. With these reservations, the milk-free foods are valuable in the dietetic treatment of selected cases of infantile eczema. They are by no means a cure-all, for there are many other causes of eczema which have nothing to do with milk.

The food sensitivities represent often a transient phase of abnormal immunology through which the infant may pass in a few months, and many tend towards recovery during the second year. At this time they can often take with impunity some of the foods to which they were previously clinically sensitive, although their skin tests may persist. However, some may retain their clinical sensitivity to certain foods for many years. According to Moro about 6 per cent continue with eczema all during childhood and even into adult life. At this period sensitivity to environmental allergens becomes more frequent.

In the treatment of infantile eczema the immunologic approach is not the whole story by any means. Skilled local treatment is many times of equal or greater importance, but inasmuch as the subject is allergy, I have stressed the allergic phase more than is justified.

It has become popular to say that many bottle-fed infants who suffer from malnutrition, vomiting, colic, diarrhea, and pylorospasm, are allergic to cow's milk. Some of this must be true, for so many people have said it, but I have seen but a few of these cases myself; and while I quite agree that sometimes some of these symptoms may be caused by allergy, I do not believe that they are commonly so caused.

There is another and very definite type of milk-allergy in early infancy: that of the breast fed baby who goes into shock and collapse, always with vomiting, and often with diarrhea, when he first takes even the smallest amount of cow's milk, so that it is obvious that he cannot be fed it. There have been reported in the literature four deaths from the ingestion of small amounts of milk. These babies are not likely to have eczema, and scratch tests to milk are usually, but not always, negative.

In contrast to those with eczema, almost all of this group can take goat's milk without symptoms. I have seen only five babies of this type in 24 years, but have been able to collect fairly accurate data of twenty others from the literature and from personal communications. Of the twenty-five, goat's milk was tried in sixteen, and was tolerated in every instance. The sensitization here is apparently clean-cut and sharp to the species specific factor of cow lactalbumin alone. It seems likely that the immunology of these infants is somewhat different than in those with eczema, although there are scarcely any data available. In the blood serum of the only one that I have been able to examine, reagins to cow's milk were absent, although shock was quickly pro-

duced by the taking of only a few drops of milk. The time conditions of antigenic exposure are quite different than in those with eczema, which possibly accounts for the clinical and immunologic differences.

The eczematous infants are taking large amounts of milk each day, and thrive except for the eczema. They are continually exposed to their allergen, and have become mildly sensitized, and perhaps partially immunized. The shock cases, on the other hand, have never come into contact with cow's milk except possibly in utero or during the neonatal period. When they are exposed to it again at the time of weaning, after a long period of abstinence, they react so violently that it is quite impossible for them to be raised on it. The situation here seems more closely analogous to animal anaphylaxis, and suggests in a striking manner the variations in degree and type of sensitization that may be brought about possibly by differences in the time interval and frequency of exposures. This seems to me of fundamental importance in any consideration of the mechanism of sensitization.

There are admitted frequently to the wards of every large children's service, children between the ages of 4 and 12 years, who have recurrent attacks of abdominal pain. These children are studied to rule out the possibility of tubercular abdominal lymph nodes, chronic appendicitis (if there is such a thing), pyelitis, kidney stone, or various anatomical anomalies of the digestive tract. It is not common to find a cause for the attacks of pain, and they are often discharged without any diagnosis having been made, and are lost track of. Some of these children have food allergy, but I think that such a diagnosis should be made with extreme caution and only after every other possibility has been excluded. Furthermore, unless the pain comes at frequent intervals, or unless the history points to some definite food, it is not satisfactory to study the possibility of food allergy while they are in the hospital; it takes too long. Skin tests are often negative, and it is in this type of patient that elimination diets may be of value. I do not like complicated systems of elimination diets; one gets tangled up in them. It has seemed to me better to put the child on a very simple diet containing only a few foods which rarely cause allergic symptoms, and which have given negative intracutaneous skin tests. If the pain is not relieved, the attack was probably not due to allergy; if it is relieved, suspected foods are added one at a time and results noted. I have seen a very few children in whom such attacks of pain were of allergic

origin. The child with asthma or eczema who has violent gastrointestinal symptoms if he eats food to which he is already known to be sensitive, is in a different category, and offers no diagnostic difficulty.

I cannot believe that recurrent or cyclic vomiting is commonly caused by allergy: there is too much evidence that it is primarily a metabolic disorder. The occurrence of acetone in the urine often before the vomiting begins, the often low blood sugar, the prompt cure by the intravenous injection of glucose and insulin, and the fact that it may be produced artificially in susceptible children by a ketogenic diet —all indicate its metabolic origin although it is, to be sure, but imperfectly understood.

The paralysis which may occur after the administration of tetanus antitoxin is witness to the fact that allergy may affect the nervous system; and, as Foster Kennedy pointed out in an admirable address here last year, the essential lesion of allergy is edema, and if there is edema in or around nerve tissue the function of that tissue will be disturbed. There can be no doubt that some cases of migraine are allergic in origin, although in my experience this disorder is not common in children. However, I have seen recently one boy entirely cured of a long-standing and severe hereditary migraine by the omission of wheat, chocolate and celery from the diet.

In short, there is a miscellaneous group of somewhat obscure conditions in which food allergy may be sometimes operative, but I am afraid that some of the more progressive allergists may have made too much progress in some of these matters. I think the more conservative ones would agree that the diagnosis of food allergy in such conditions should be made only with great caution, and only when the evidence is incontrovertible: there are too many other causes for such symptoms, particularly in the digestive tract. In the selected material of the allergist, food allergy may be common: in unselected material it is not. If allergy is to keep a good reputation, it must not claim too much, and must tread softly and speak modestly when dealing with this borderline group.

Respiratory allergy is not so common in early infancy as in later infancy and childhood, but even young infants may have asthma or vasomotor rhinitis. Also, there is a growing belief that the so-called capillary bronchitis of young infants, which has always been so amenable to adrenalin, may be allergic. The child with frequent colds,

particularly if they occur all the year round, may be suffering from allergic rhinitis, and such a possibility is worth investigating. However, I have the impression that the allergic child is more susceptible to ordinary infectious colds than is the normal child.

Asthma is to the older child what eczema is to the infant. The chief differences between asthma in the child and in the adult are that a higher proportion of cases in children is allergic, and that, while respiratory infection is important as a co-existing or predisposing factor, it is not so important as in the adult asthmatic of long standing, with his chronic bronchitis, emphysema, and permanently deformed chest. The greater the chronic infection, the greater the permanent damage, the worse the prognosis: the prognosis as to relief or even cure is therefore better in the child than in the adult.

While food allergy may play a part in asthma, environmental allergens are, as a rule, more important. I think most allergists would agree that many positive skin tests to foods in older children are simply residues of past clinical sensitivities, without significance, for it is common for a skin test to persist for a considerable time after the clinical sensitivity has been lost. Furthermore, some positive skin tests may never have been of etiologic significance. It is usually a mistake to omit a large number of foods from the diet of an older asthmatic child, no matter what the skin tests show. One finds occasionally, but all too rarely, an asthma that is due to one definite allergen and one alone. More often the sensitivity is multiple, and a strongly allergic child may give many positive tests to foods and inhalants, which represent all degrees of clinical sensitivity. Some food proteins which previously passed unsplit through the intestinal mucosa, do so no longer. Some which caused symptoms at one year do not at five years, even if unchanged protein is absorbed. Others may still be in the acutely hypersensitive phase. The allergic child is never static; his allergic pattern is continuously changing; he is becoming acclimated to some allergens and sensitized to others.

It is not easy to determine which skin tests are of clinical significance, and no allergic individual can be dealt with correctly solely on the basis of his skin tests. The only real criterion is production of symptoms on exposure to the allergen. This requires careful history taking, accurate clinical observation, common sense, and the ability to evaluate the relative importance of data; to see the whole forest with-

out looking too hard at one tree, which after all is perhaps the most important thing for the practice of good medicine, no matter in what field.

In brief, the basic immunologic treatment in many cases of asthma in children is to avoid a very few foods and, insofar as possible, all suspected environmental allergens; and, when indicated, to inject nonspecific respiratory vaccines; or in winter, house dust; or in summer, pollens.

Any allergic child should be under observation not for weeks or months, but for years. He overcomes some sensitivities, but acquires new ones. He has a constitutional defect, just as a diabetic has, which cannot be changed by any doctor. However, his symptoms can usually be controlled, and he has often—but by no means always—the ability to overcome his sensitivities and cure himself in the course of time. The stage of sensitization in the relations of any young individual with allergenic material is only part of the picture—the most spectacular, to be sure, because he has symptoms during this stage. In order to obtain a complete view of the whole process, his immunologic status after he has passed through the phase of sensitivity needs to be more clearly understood. This tendency to natural acclimatization, development of tolerance, or immunization, if it is permissible to call it so, is perhaps the most striking and important observation that can be drawn from a study of allergy in the young individual. I should like to know better the details of the mechanism by which it is brought about.

ANALYSIS OF MATERNAL DEATHS AND HOSPITAL OBSTETRICAL STATISTICS IN NEW YORK COUNTY*

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THE Special Committee on Maternal Welfare of the Medical Society of the County of New York organized a study on Maternal Mortality in May, 1937. This is in reality a continuation of the study of all puerperal deaths in New York City, 1930-1932, by the Committee on Public Health Relations of The New York Academy of Medicine. This study was published in 1933 by The Commonwealth Fund under the title: Maternal Mortality in New York City. The analysis group consists of two representatives of each voluntary and municipal hospital in New York County, one of the five counties (Borough of Manhattan) constituting the City of New York.

Meetings are held monthly, and the average attendance varies from eighteen to forty. From ten to fifteen cases are studied at each meeting. These cases are obtained through the coöperation of the Health Department, which gives us copies of death certificates concerned with pregnancy and childbirth. A questionnaire is then sent to the hospital or physician connected with the case. In the very rare instance of a midwife attendant, personal contact is made. The Maternity Centre Association has been of great value in the clerical work attached to this study. Since the inception of this work, a total of 171 cases has been studied.

Before presenting an analysis of our cases, it is interesting to study a chart from the Department of Health analyzing the maternal deaths in

* This report of the Committee on Maternal Welfare of the Medical Society of the County of New York was presented March 28, 1939 before the Section of Obstetrics and Gynecology of The New York Academy of Medicine.

the City of New York for the last four years. As may be seen, there has been a progressive decrease in all causes of death. The mortality rate per 1000 live births has decreased 33 per cent.

New York State has also shown a decrease of 33 per cent. The United States has shown a diminution in its maternal mortality rate for the last seven years. In 1930 it was 6.7, and in 1937 it was 4.88—a diminution of 27 per cent. There are only four countries with a higher mortality.

The Quarterly Bulletin of the Department of Health of the City of New York in its February 1939 issue makes the following statement:

"It is of interest to study the course of the mortality of mothers in childbirth, a problem to which the Advisory Obstetric Council devoted its first attention. For many years the maternal death rate had remained almost unchanged. Thirty years ago it was 4.8 per 1000 live births; ten years later it was the same. In 1928 it had risen to 5.3 and by 1933 to 6.4. Although the maternal mortality rate had fluctuated somewhat in individual years, it would appear that the marked reduction in the rate during the past few years, reflects the excellent work done by the county medical societies in coöperation with the Department of Health."

When one studies Chart I, one may see that puerperal septicemia has decreased by 30 per cent. In New York County the reduction is 68 per cent. In classification No. 148 (Puerperal phlegmasia, alba dolens) are included all cases of puerperal shock and embolus. These have diminished but little. The difficulty in obtaining autopsies makes it very hard to verify the causes of death. Also to be noted is the slight change in the toxemic death rate.

Analysis of Maternal Deaths

The 171 cases which we studied occurred during a period of twenty months, from May 1937 to February 1939. We have divided them into four classes, as shown in Chart II.

Under the designation, Obstetrical, are included cases in which the most important problem was primarily concerned with childbirth and pregnancy, and not with any other medical or surgical condition. Most of the non-puerperal deaths were classified as maternal deaths by the Health Department, which follows the rules promulgated by the Federal Bureau of Census. Thus the patients with spinal meningitis and bacterial endocarditis who died undelivered were put in the group of puerperal

CHART I

CITY OF NEW YORK DEATHS FROM PUERPERAL CAUSES, BY BOROUGH OF RESIDENCE

1935 - 1938*

Int. List No.	Cause of Death	City of New York				Manhattan				Bronx				Brooklyn				Queens				Richmond			
		1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*	1935	1936	1937	1938*
140	Abortion with septic condition	88	69	61	49—	40	39	31	18—	8	6	5	7+	31	14	14	14•	9	10	10	10•	0	0	1	0—
141	Abortion without mention of sepsis	30	11	12	9—	14	5	0	3+	2	1	2	1—	12	5	7	3—	2	0	2	1—	0	0	1	1•
142	Ectopic gestation	28	29	33	19—	9	12	10	9—	2	5	8	3—	15	7	12	4—	2	2	3	3•	0	3	0	0•
143	Other accidents of pregnancy	4	3	5	2—	1	1	2	0—	1	0	0	0•	1	1	3	0—	0	1	0	2+	1	0	0	0•
144	Puerperal hemorrhage	74	57	55	63+	27	14	10	16+	11	9	12	6—	20	25	21	19—	15	9	12	14+	1	0	0	8+
145	Puerperal septicemia	86	91	80	61—	25	25	26	8—	10	13	14	13—	40	37	29	26—	8	14	11	13+	3	2	0	1+
146	Puerperal albuminuria and eclampsia	39	46	39	31—	9	10	12	5—	5	13	4	9+	12	16	16	11—	12	6	7	5—	1	1	0	1+
147	Other toxemias of pregnancy	19	14	15	18+	6	3	3	5+	2	3	2	5+	8	6	9	5—	2	2	1	3+	1	0	0	0•
148	Puerperal phlegmasia, alba dolens	29	23	18	25+	8	9	3	5+	5	4	3	3•	9	8	10	11+	7	2	1	6+	0	0	1	0—
149	Other accidents of childbirth	114	114	86	78—	32	36	12	20+	17	23	23	11—	44	36	34	32—	18	19	16	15—	3	0	1	0—
150	Other conditions of puerperal state	12	2	4	0—	6	1	0	0—	0	0	1	0—	5	1	3	0—	1	0	0	0•	0	0	0	0•
	Total puerperal causes	523	459	408	355—	177	155	109	89—	63	77	74	58—	197	156	158	125—	76	65	63	72+	10	6	4	11+
	Mortality rate per 1000 live births	5.2	4.7	4.0	3.5				3.5																

* Provisional • Same as 1937 — Decrease in 1938—33% + Increase in 1938

CHART II

CLASSIFICATION OF 171 MATERNAL DEATHS, BY CAUSE

		Number	*Per cent*
Obstetrical		104	60.8
Extrauterine		12	7.
One full term abdominal pregnancy			
Post abortum		32	18.7
With sepsis	27 or 84 per cent		
Others	5 or 16 per cent		
Non-Puerperal*		23	13.4
Pneumonia	6		
Cardiac	4		
Bacterial Endocarditis	1		
Thyrotoxicosis	1		
Spinal meningitis	1		
Kidney abscess	1		
Acute appendicitis	1		
Chronic nephritis	2		
Ovarian abscess	1		
Miscellaneous	5		

* Cases where pregnancy and labor had no connection with the death or were contributory with another primary factor.

sepsis, because there was an associated fever. On the other hand a cesarean section for premature separation of the placenta in which autopsy showed acute yellow atrophy of liver, was classified as non-maternal. However, conferences were held last year for the purpose of making a new classification of the causes of death, in which contributory factors will be evaluated differently.

Most of the cases of abortion were induced and died of sepsis. However, a case of abortion with pernicious vomiting of pregnancy was classified as an obstetrical death. Under extrauterine pregnancy is included one full term abdominal pregnancy with the placenta left in the abdomen; death was due to the toxemia caused by the absorption of the placenta.

At the meetings of the Mortality Analysis Committee, detailed discussion was principally concerned with the 104 obstetrical deaths analyzed in Charts III to IX. These charts do not analyze the non-puerperal, abortive or ectopic deaths.

CHART III

CLASSIFICATION OF 104 OBSTETRICAL DEATHS, BY TYPE OF HOSPITALIZATION, ATTENDANCE AND PRENATAL CARE

	Number	Per cent
Place of Delivery		
Voluntary hospitals	59	57.
Municipal hospitals	22	21.
Proprietary hospitals	18	16.3
Home	5	4.7
Attendants		
Obstetricians and gynecologists	66	63.5
Obstetricians and gynecologists and intern	7	6.7
Obstetricians and gynecologists and general practitioner	5	4.8
General practitioner	9	8.6
Intern	12	11.5
Midwife	2	1.9
General surgeon	1	
Unattended	2	1.9
Prenatal Care		
Adequate	89	85.6
No care	15	14.4
(Only two of those with no care died of toxemia)		

Fifty-seven per cent of the obstetrical deaths were delivered in the voluntary hospitals. Only 4.7 per cent were delivered at home.

ATTENDANTS

Sixty-three per cent of the attendants were specialists in obstetrics. Another 11.5 per cent of the patients were attended by interns and general practitioners with the assistance of an obstetrician. There were only two midwife attendants. Thus it can be stated that 75 per cent of the cases received "the best possible skill both in diagnosis and treatment which the community could make available." This is the criterion of The New York Academy of Medicine study in 1933, already cited.

CHART IV

CLASSIFICATION OF 104 PUERPERAL DEATHS, BY COLOR

	Number	*Per cent*
White	95	91.
Colored	9	9.

For the year 1938 in New York County, white births totaled 27,280 or 87 per cent, colored births totaled 3,659 or 13 per cent.

PUERPERAL DEATHS BY COLOR IN 1938—Greater New York City

				Rates (per 10,000 live births)	
	Total	*White*	*Colored*	*White*	*Colored*
Abortions with sepsis	50	31	19	3.3	24.8
Ectopic	19	12	7	1.3	9.1
Puerperal hemorrhage	63	57	6	6.0	7.8
Puerperal sepsis	61	54	7	5.7	9.1
Albuminuria and eclamp.	31	27	4	2.9	5.2
Other accidents of childbirth	79	73	6	7.7	7.8
All other puerperal causes	57	54	3	5.4	3.9
TOTAL	357	305	52	32.3	67.9

SOME VITAL STATISTICS FOR THE CENTRAL HARLEM HEALTH CENTER DISTRICT IN COMPARISON WITH RATE FOR NEW YORK CITY

	1934	*1935*	*1936*	*1937*	*1938*
Maternal mortality rate per 1000 live births	9.2	14.6	17.9	8.5	5.4
New York City	5.9	5.1	4.7	4.0	3.3

PRENATAL CARE

The question of prenatal care does not seem to be a principal factor, as only 14 per cent lacked adequate prenatal care. This is in accordance with the views expressed by Aranow*: "That while prenatal care is extremely useful in avoiding certain obstetrical complications, its importance in the prevention of maternal mortality has been overemphasized." However, it must be admitted that no thorough study was made of how adequate that care was.

* Aranow, H. Maternal mortality, *Preventive Medicine*, 1937, *7*: 113.

Color

Ninety-one per cent of the deaths were of white women and 9 per cent of colored. Chart IV (Department of Health) shows the causes of death according to color for the year 1938. The septic abortion death rate in colored women is more than seven times that prevalent in white women and the puerperal sepsis rate almost double. The toxemic death rate is nearly twice that of white. In this respect, New York City parallels the conditions in the Southern States. In Chart IV there is a comparison of the death rates in the Central Harlem Health Center District (which is almost entirely colored) with that of the entire city. The death rate in colored women has dropped almost 50 per cent in five years.

Methods of Delivery

Chart V shows the types of delivery and causes of death. More than half of the cases were operative, excluding the breech deliveries, and more than half (55 per cent) of the operative cases were cesarean sections. However, in reference to this question it is well to quote what Israel said in his study of maternal deaths in Erie County:

"Death rates following major operative techniques (version and cesarean section) are definitely higher than those following normal and low forceps deliveries; also, the rates following cesarean sections are definitely higher than those following versions. From the data given no categorical statement can be made that major operative procedures are causes of higher puerperal mortality rates; it can definitely be stated, however, that the two are highly correlated, that greater chance for the mother's death is associated with greater use of such techniques. The real cause of such deaths may be the procedure used; on the other hand, it is equally likely that the complicating conditions which lead to the use of such measures would have caused death in any event. It is probable that the use of these methods has prevented many deaths. The presence of this high degree of correlation between major operative techniques and a high mortality rate complicates rather than simplifies the procedure. In order adequately to determine the relation of such obstetrical methods to the death rate, a statistical study of complicating factors in a large number of unselected cases should be made. Only after such a controlled study, eliminating the effect of such factors, can definite conclusions regarding the importance of such techniques as causes of death per cent,

CHART V

CAUSES OF DEATH AND METHODS OF DELIVERY OF 104 OBSTETRICAL CASES

Cause of Death			*Method of Delivery*						
			Spontaneous	*Forceps*	*Cesarean Section*	*Breech Extraction*	*Version Breech Extraction*	*Spontaneous Rupture Uterus*	*Not Delivered*
	Number	Per cent	31 Cases 30 per cent	24 Cases 23 per cent	34 Cases 32.7 per cent	6 Cases 5.8 per cent	3 Cases 2.9 per cent	2 Cases 1.9 per cent	4 Cases 3.8 per cent
Hemorrhage	35	33.6	12	6	8	4*,**	1***	2	2
Shock	3	2.9		3					
Sepsis	24	23.0	7	2	13		2		
Pneumonia	6	5.7	1		5				
Toxemia	14	13.4	8	2	2				2
Cardiac	5	4.8	1	1	2	1			
Embolus	7	6.7	1	4	1	1			
Anesthesia asphyxia	6	5.7		4	2				
Tuberculosis	1		1						
Transfusion reaction	1			1					
Essential hypertension—Pulmonary edema	1				1				
Rupture of bladder, lumbar abscess—embolus	1			1					
TOTAL	104								

* From cervical laceration

** Vomitus in lungs in one case

*** Hemorrhage followed by sepsis

be judged. In connection with this question of primacy of delivery methods as causes of death, it is noteworthy that the scheme of classification of death certificates of puerperal deaths given in the Manual of Joint Causes of Death, the official standard of the Census Bureau, gives precedence to the complicating condition for which the operative technique was used, rather than to the operation itself."

Hemorrhage accounts for 33 per cent of the maternal deaths and is thus the principal cause in New York County. This primacy of hemorrhage may be due to the diminution in the sepsis incidence. The wide use of blood transfusion and parenteral administration of fluids has apparently had no influence on the deaths from hemorrhage. There may be a need for a revaluation of the methods used in the treatment of the third stage of labor. Perhaps the amount of hemorrhage is underestimated and more accurate methods to determine the quantity of blood lost should be employed. This whole subject is now being investigated by a special committee appointed by the New York City Board of Health.

In cesarean section, sepsis and pneumonia (the latter may be classified as a septicemia) cause more than half of the deaths in that method of delivery.

Toxemia caused 13.4 per cent of the deaths. Only three were colored, and five had inadequate prenatal care.

Heart disease is an important cause of puerperal deaths. It should be evident that pregnant women with cardiac disease need specialized care.

Anesthesia was a cause of six deaths; four of these during forceps delivery. Our Committee has recommended the employment of well-trained anesthetists in all obstetrical cases.

The case of tuberculosis was noted as an obstetrical death because it was not diagnosed during the early antepartum visits to the prenatal clinic.

Causes of Death and Methods of Delivery in Relation to Complications of Pregnancy and Labor

Charts VI-IX

(Pages 413-415)

CHART VI

CESAREAN SECTION

34 Cases or 34.7 per cent of 104 Obstetrical Cases

Classical	13
Low flap	20
Peritoneal exclusion	1

Cause of Death	
Sepsis	13
Pneumonia	5
Hemorrhage	8
Toxemia	2
Essential hypertension — pulmonary edema	1
Embolus	1
Cardiac failure	2
Aspiration asphyxia—anesthesia	2

Complicating Conditions	
Prolonged labor	7
Toxemia	4
Placenta previa	4
Cardiac disease	4
Contracted pelvis	3
Previous cesarean	3
Premature separation of the placenta	1
Primip unengaged head	1
Elderly para 3 and fibroids	1
Elderly primip and fibroids	2
Bicornuate uterus—transverse presentation	1
Hemiplegia—essential hypertension	1
Previous difficult labors	1

CHART VII

FORCEPS

24 Cases or 23 per cent of 104 Obstetrical Cases

Low	14
Mid	10

Cause of Death	
Anesthesia	4
Hemorrhage	6
Shock	3
Sepsis	2
Toxemia	2
Embolism	4
Cardiac failure	1
Rupture of bladder, lumbar abscess, embolus	1
Transfusion reaction	1

Complicating Conditions	
Prophylactic, or low forceps	9
Prolonged labor	9
Eclampsia and toxemia	4
Low implantation and partial separation of placenta	1
Cardiac disease	1

CHART VIII

SPONTANEOUS BIRTHS

31 Cases or 30 per cent of 104 Obstetrical Cases

Cause of Death		*Complicating Conditions*	
Hemorrhage	12	Antepartum sepsis	2
Sepsis	7	Cardiac disease	4
Toxemia	8	No pathology	7
Embolus	1	Eclampsia and toxemia	10
Pneumonia	1	Retained placenta (2 syphilitic)	4
Cardiac failure	1	Post partum psychosis and pneumonia	1
Tuberculosis	1	Low implantation of placenta	1
		Tuberculosis	1
		Diabetes, pyelitis	1

In a consideration of the complicating conditions in operative deliveries, the following facts must be noted:

Cesarean section:

(a) In 20 per cent of the cases the indication was prolonged labor. Numerous studies have shown that the danger of a fatality in cesarean section increases with the number of hours the patient has been in labor (including the cases that have had no vaginal examinations).

(b) Twenty of the thirty-four cases of cesarean section were of the low flap type.

(c) Only a small proportion of the cases were for contracted pelvis.

Forceps deliveries:

More than one-third were prophylactic or low forceps. In this group two of the deaths were due to anesthesia. However, it should be stressed that forceps deliveries per se are not to be considered as the cause of death.

Breech extraction:

Four of these patients died as a result of hemorrhage from a cervical laceration, which was not recognized immediately after delivery.

Edward M. Davis in his address on "Professional Resources and Ability to Provide Good Maternal Care," at the Washington Conference in 1938 states:

CHART IX

BREECH EXTRACTION

6 Cases or 5.8 per cent of 104 Obstetrical Cases

Cause of Death	*Complicating Conditions*
Hemorrhage, shock, cervical laceration vomitus in lungs	Twins
Hemorrhage, cervical laceration	Low implantation of placenta
Hemorrhage, cervical laceration	Transverse presentation
Hemorrhage, cervical laceration	Syphilis
Embolus (8th day)	Chronic nephritis, retained placenta (24 hours)
Cardiac death	Mild toxemia

VERSION AND BREECH EXTRACTION

3 Cases

Cause of Death	*Complicating Conditions*
Sepsis	Central placenta previa, 5½ months, Braxton-Hicks version, incision of cervix
Hemorrhage, sepsis, unrecognized cervical laceration	
Sepsis	Placenta previa, bag induction, hysterectomy
	Brow presentation, forceps delivery attempted

SPONTANEOUS RUPTURE OF UTERUS

2 Cases

Cause of Death	*Complicating Conditions*
Hemorrhage	39 year Para IV, hysterectomy
Hemorrhage	Para V, 31 hours in labor in hospital, hysterectomy

NOT DELIVERED

4 Cases

Cause of Death	*Complicating Conditions*
1. Toxemia	Eclampsia
2. Massive accidental hemorrhage	Brought to hospital in shock
3. Toxemia	Pernicious vomiting of pregnancy
4. Found dead at home with rupture of uterus (two previous cesareans)	

"The family practitioner in charge of an obstetric patient may be in need of consultation when complications arise. His inability to cope with these complications is no reflection on his training, for in all likelihood he has made the most of these opportunities, but they have not been sufficient to prepare him to meet emergencies."

When one considers the fact that serious obstetric complications occur rather rarely, one can realize the large number of patients the average attendant would have to see in order to develop sufficient skill to treat these complications.

E. D. Plass in an article in the Journal of the American Medical Association (Aug. 27, 1938) states:

"The struggle to reduce maternal death rates, when viewed in terms of general practice, involves experiences so isolated that their significance may well be lost. If a practitioner has fifty obstetric cases annually, he will observe only one serious complication each year and will not have more than one maternal death every four or five years. Such isolated experiences are not impressive and are soon forgotten. Moreover, their rarity prevents the physician from acquiring the knowledge of diagnosis and treatment essential to saving these occasional patients. Under prevailing conditions the wonder is not that so many women die as a result of child bearing, but that so many are carried safely through the perils of procreation."

Before stating our conclusions we present the study which follows of cesarean sections in New York County, prepared by Thomas J. Duffield and Sylvia L. Parker:

In March, 1938, new forms of birth and fetal death (stillbirth) certificates were introduced in the City of New York. These new forms included a supplementary confidential medical report, on the back of the certificate, which called for information concerning the period of gestation, weight and length of the infant (fetus) at birth, complications of pregnancy and of labor, mode of delivery, method of induction of labor, if any, etc. Mode of delivery had previously been collected with regard to live births but not in connection with stillbirths.

For the year 1938, therefore, information regarding mode of delivery is available for 97 per cent of the infants born alive in the County of New York (Borough of Manhattan). Because the old forms of stillbirth certificates did not call for any information on the mode of delivery and because the new forms of fetal death certificates came into use more

slowly than did the new birth certificates, information regarding the mode of delivery of stillborn fetuses was so incomplete during 1938 that the data presented in this paper are based solely on live births, although it is obvious that stillbirths as well as live births figure in both maternal mortality and cesarean sections. At a later date we expect to present data on puerperal mortality and mode of delivery based on the entire recorded exposure to risk.

The total number of live births recorded in Manhattan (New York County) in 1938, the number for which the mode of delivery was stated, and the percentage of infants born alive that were delivered by cesarean section, by color and place of birth, is presented in Chart X. This information is presented for three groups of hospitals: municipal, voluntary and proprietary.

Chart XI shows the variations in individual hospitals in the three classifications, listed in descending order of the percentage of cesarean deliveries among white live births. With the exception of three municipal and two voluntary hospitals, the number of colored births in any individual hospital in the city is so small that the resultant percentages, in general, lack statistical significance.

Regarding the cesarean rates shown in Charts X and XI, it should be pointed out that the decision to use the numbers of total live births rather than the number of live births with mode of delivery stated as the basis for these rates was made in the belief that for the purposes of this paper it was preferable to present cesarean rates which were the minimum values which the actual rates could have, if mode of delivery were known for every birth. That is, it can be stated for each hospital, at least this percentage of the deliveries was by cesarean section. To use percentages based on the numbers for which the mode of delivery was stated would amount to assuming that the cesarean rate among the deliveries with mode not stated was the same as the rate among those with mode stated.

If the proportion of deliveries by unknown mode were greater, or varied much in different groups to be compared, this would of course be a more serious question. As it is, examination of the tables shows that none of the cesarean rates would be changed much, if the rates were based on the number of births for which the mode of delivery was stated. In Table X, for example, the cesarean rates in municipal hospitals would be unchanged, those in voluntary hospitals would be raised from

CHART X

LIVE BIRTHS BY PLACE AND MODE OF DELIVERY
COUNTY OF NEW YORK (MANHATTAN)

1938

Place of Birth	WHITE				COLORED			
	Live Births		*Cesarean Sections*		*Live Births*		*Cesarean Sections*	
	Total	With mode of delivery stated	Number	Per cent of total live births	Total	With mode of delivery stated	Number	Per cent of total live births
5 Municipal Hospitals†	2879	2854	46	1.6	2681	2665	31	1.2
24 Voluntary Hospitals†	20841	20514	794	3.8	918	910	38	4.1
11 Proprietary Hospitals†	3046	2889	121	4.0	17	16	1	*
Other Hospitals‡	514	499	16	3.1	43	39	3	*
Total Hospitals	27280	26756	977	3.6	3659	3630	73	2.0
Home	1528	1169	0	0.0	680	499	0	0.0
GRAND TOTAL	28808	27925	977	3.4	4339	4129	73	1.7

† Hospitals with more than 150 live births each in 1938.

‡ Hospitals with less than 150 live births each in 1938.

* Number of births too small to allow computation of rate.

CHART XI

CESAREAN SECTIONS IN HOSPITALS HAVING MORE THAN 150 LIVE BIRTHS EACH IN 1938 NEW YORK COUNTY (MANHATTAN)

Place of birth		WHITE				COLORED			
		Live births		Cesarean sections		Live births		Cesarean sections	
		Total	With mode of delivery stated	Number	Per cent of total live births	Total	With mode of delivery stated	Number	Per cent of total live births
5 Municipal Hospitals	Total	2879	2854	46	1.6	2681	2665	31	1.2
	A	429	428	9	2.1	94	94	2	2.1
	B	332	330	6	1.8	2213	2200	22	1.0
	C	620	614	10	1.6	162	160	3	1.9
	D	1208	1199	18	1.5	191	190	4	2.1
	E	290	283	3	1.0	21	21	0	*
24 Voluntary Hospitals	Total	20841	20514	794	3.8	918	910	38	4.1
	A	532	527	45	8.5	6	6	1	*
	B	472	469	36	7.6	186	185	6	3.2
	C	974	962	63	6.5	134	133	3	2.2
	D	1624	1614	98	6.0	9	8	0	*
	E	828	814	45	5.4	2	1	0	*
	F	841	839	38	4.5	1	1	0	*
	G	537	534	24	4.5	31	31	0	0.0
	H	2157	2154	92	4.3	315	315	19	6.0
	I	586	565	24	4.1	2	2	0	*
	J	459	446	19	4.1	7	7	0	*
	K	1020	1013	41	4.0	0	0	0	*
	L	1062	1055	40	3.8	26	25	2	*
	M	314	311	11	3.5	17	17	0	*
	N	428	415	14	3.3	1	1	0	*
	O	2781	2781	85	3.1	112	112	5	4.5
	P	392	379	12	3.1	17	17	0	*
	Q	464	422	13	2.8	1	0	0	*
	R	815	814	22	2.7	20	20	2	*
	S	552	533	14	2.5	1	1	0	*
	T	876	839	19	2.2	7	6	0	*
	U	1097	1014	19	1.7	19	18	0	*
	V	814	808	12	1.5	1	1	0	*
	W	954	950	7	0.7	0	0	0	*
	X	262	256	1	0.4	3	3	0	*
11 Proprietary Hospitals	Total	3046	2889	121	4.0	17	16	1	*
	A	241	240	19	7.9	0	0	0	*
	B	362	334	27	7.5	1	1	1	*
	C	232	232	13	5.6	2	2	0	*
	D	596	515	28	4.7	0	0	0	*
	E	399	382	16	4.0	0	0	0	*
	F	144	142	5	3.5	6	6	0	*
	G	189	189	6	3.2	2	1	0	*
	H	234	225	5	2.1	0	0	0	*
	I	169	159	1	0.6	2	2	0	*
	J	315	307	1	0.3	2	2	0	*
	K	165	164	0	0.0	2	2	0	*

* Number of births too small to allow computation of rate.

CHART XII

NEW YORK COUNTY (MANHATTAN) MATERNAL MORTALITY*

1938

Place of Birth	WHITE			COLORED		
	Live births	Number of deaths*	Rate per 1000 live births	Live births	Number of deaths	Rate per 1000 live births
5 Municipal Hospitals†	2879	17	5.9	2681	8	3.0
24 Voluntary Hospitals†	20841	38	1.8	918	4	4.4**
11 Proprietary Hospitals†	3046	10	3.3	17	0	0.0**
Other Hospitals‡	514	3	5.8**	43	0	0.0**
Total Hospitals	27280	68	2.5	3659	12	3.3
Home	1528	2	1.3**	680	0	0.0**
GRAND TOTAL	28808	70	2.4	4339	12	2.8

* Puerperal Mortality, exclusive of deaths associated with abortion or ectopic gestation.
** Based on too small numbers for rates to have statistical significance.
† Hospitals with more than 150 live births each.
‡ Hospitals with less than 150 live births each.

3.8 and 4.1 to 3.9 and 4.2, respectively. The largest change would be in the white rate in proprietary hospitals, which would be raised from 4.0 to 4.2. In Chart XI, the greatest changes would be in the white rates for proprietary hospitals B and D where the rates would become 8.1 and 5.4, respectively, instead of 7.5 and 4.7. Conclusions drawn from these cesarean rates were subjected to the most stringent test possible, that is, examining whether the conclusion would still hold if, while keeping the *higher* of two cesarean rates at its minimum possible value, the *lower* of the two rates were given its maximum value by assuming that all the deliveries of unknown mode in that group were cesareans.

The five municipal hospitals as a group reported cesarean deliveries of 1.6 per cent of the infants born alive to white mothers and 1.2 per cent to colored mothers. In the voluntary hospitals the percentages among white and colored were 3.8 and 4.1, respectively. These figures indicate that cesarean section is much more frequently practiced in the

voluntary than in the municipal hospitals. This comparison holds even under the stringent test described above. That is, assuming that in municipal hospitals every one of the 25 live births to white mothers for which the mode of delivery was not stated was a cesarean delivery, there would have been 71 cesarean sections, giving a rate of 2.5 per 100 live births. This figure is still considerably below the rate of 3.8 per 100 live births in voluntary hospitals, though the rate of 3.8 in voluntary hospitals treats the 327 live births for which the mode of delivery was not stated as if none of them was a cesarean. The corresponding test of the cesarean rate for colored mothers, assuming every one of the 16 unknowns in municipal hospitals to have been a cesarean, would make 47 cesareans, giving a rate of 1.8 per 100 live births, in comparison with the minimum rate of 4.1 in voluntary hospitals.

For any particular type of hospital the cesarean rates were not significantly different for white and for colored mothers. For *all* white mothers, on the other hand, the cesarean rate, 3.4 per cent, was twice as high as that for all colored mothers, 1.7 per cent. This is an apparent contradiction to the previous statement. It is easily explained, however, by the fact that 65 per cent of the *colored* live births in Manhattan occurred in the municipal hospitals where the cesarean rate was low, whereas only 10 per cent of the *white* live births occurred in the municipal hospitals.

Detailed study of the maternal mortality records for the individual hospitals does not show any relationship between the percentage of cesarean sections performed and the mortality experienced. The figures are not included in Chart XI as the numbers are too small to justify any computation of rates. Chart XII gives, however, the mortality figures for groups of hospitals. It is to be noted that in the municipal hospitals which obtain a larger proportion of their cases as emergency admissions through ambulance calls, the maternal mortality among white mothers was higher than in either the voluntary or the proprietary hospitals. This is in agreement with other statistics available where a distinction is made between patients receiving adequate prenatal care and those admitted as emergencies. The higher maternal death rate in municipal hospitals occurs in spite of the very much lower cesarean rate in those institutions. The maternal mortality rate for colored mothers, however, was not higher in municipal hospitals than in voluntary hospitals.

As a final conclusion to be drawn from the above tables, it should

be emphasized that when abortions and ectopics are excluded, the maternal mortality rate for white mothers was only 2.4 per 1,000 live births and that for colored mothers was 2.8 per 1,000 live births.

Conclusions

1) It has been said that the great progress in the practice of medicine was a result of a thorough study of autopsy material and discussion of cases at regular clinical pathological conferences. The latter term can be applied to the work of our Maternal Mortality Study Group. It can easily be seen how great is the educational value resulting from a study of maternal deaths among 30,000 annual births, which are discussed from the different viewpoints of the representatives of twenty-five hospitals, and four medical colleges.

2) When one considers that about 90 per cent of obstetrical cases will be delivered without any difficulty, and that the complications and obstetrical emergencies occur so rarely, one can readily see how difficult it is to acquire the art of obstetrics. In addition, the facilities for the teaching of the student, the intern as well as the specialist, are very limited. Perhaps the answer to this problem may be compulsory consultations in all difficult obstetrical cases. This policy has already been advocated by a number of medical societies (Kings County and Philadelphia) and has received practical support from the Federal Government.

3) It is apparent from our analysis of hospital deliveries that the cesarean rate is high in some institutions. It is also true that more than one-third of the obstetrical deaths occur in cesarean section. However, the municipal hospitals, with the lowest cesarean rate, have a higher mortality rate than the voluntary and proprietary hospitals. This is probably due to the fact, that the municipal hospitals have a much larger number of ambulance emergency patients, who usually have a greater number of obstetrical complications. Perhaps there is also an economic factor, with its associated malnutrition and poor physical condition present in the municipal hospital cases.* It has been stated that obstetrics is passing through a transition stage and that with the standardization of procedures and indications for operation, this operative mortality will be still further reduced. Towards this latter end it must be evident that the work of our Mortality Analysis Group should be a great help.

We have not discussed the question of preventability of the maternal deaths. The numerous studies published on that subject in the last few

years have already produced their full value in exciting an interest in the subject of maternal mortality. However, in any popularization of the figures of preventability there should be a separation of the deaths resulting from abortion and extrauterine pregnancy, from those associated with the difficulties of childbirth and labor.

At our meetings for the analysis of cases, we discuss and vote on preventability. The question of preventability is very often difficult to decide. We feel that the greatest value to be obtained from our analysis, is that of learning from the unfortunate results before us.

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* In discussing James K. Quigley's paper on "Maternal Welfare, What Are Its Fruits?" (*Am. J. Obst. & Gyn.*, 1940, *39*: 349), the following statement was made by a Dr. James R. McCord:

"There is probably more in the problem of maternal mortality than good obstetric care. You can take any map of maternal mortality rates and you find that most of the Southern States have high rates. Also, in general, the colored rates are nearly twice as high as the whites. You might immediately say that we are not doing good obstetric work in the South.

I live in a city of approximately one-half million people, with a colored population of 150,000. We deliver about 2,200 colored women a year in our clinic in the municipal hospital. Our obstetric service is far from being a finished service but it is a conservative service. Our total operative incidence is 3.96 per cent which includes the packing of the vagina. Our forceps incidence for term and premature deliveries is 1.3 per cent; the cesarean incidence 0.46 per cent, and yet we have an uncorrected maternal mortality rate of 6.4 per 1,000 pregnancies. These women are getting good obstetric care and yet we have a tremendous mortality rate. Approximately 45 per cent of the women on our service are either illegitimately pregnant, the husband unemployed or on W.P.A.

With agriculture in the depths, negroes all over the South are moving into the larger communities where they are badly housed and ill fed. Sepsis is the killer of colored women, and certainly on our service we can conscientiously say that it is in large measure not our fault. I do not mean in the least to deprecate good obstetric care, but I do believe that permanent lowering of maternal mortality must be accompanied by a proportionately rising economic level."

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

Association for Research in Nervous and Mental Disease. *The hypothalmus and central levels of autonomic function.*
Balt., Williams, 1940, 980 p.

Bing, R. *Compendium of regional diagnosis in lesions of the brain and spinal cord.* 11. ed.
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Contribution to radiology in honor of Dr. I. Seth Hirsch by his pupils and friends, 1939.
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Oliver, O. A.; Irish, R. E. & Wood, C. R. *Labio-lingual technic; a description of the labial and lingual appliances in the treatment of malocclusion.*
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Selling, L. S. *Men against madness.*
N. Y., Greenberg, [1940], 342 p.

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Paris, Legrand, 1939, 138 p.

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Thomen, A. S. A. *Doctors don't believe it. Why should you?*
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Uslenghi, J. P.; Hofmann, H. & Heilpern, M. J. *La fotografía del estómago.*
Buenos Aires, Lopez, 1939, 215 p.

Youmans, J. B. *Essentials of the diagnostic examination.*
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Ziegler, P. F. *Textbook on sutures.*
Walpole, Mass., Lewis Mfg. Co., [1939], 70 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

APRIL 4—*The New York Academy of Medicine.* Executive session—a] Reading of the minutes; b] Vote on amendments to constitution and by-laws. ¶ The Fifteenth Hermann Michael Biggs Memorial Lecture, "Heart disease—a world problem," Paul Dudley White, Lecturer in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital. ¶ Report on election of members.

APRIL 18—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Seventh Harvey Lecture, "Morphological and Functional Alterations of the Coronary Circulation," Joseph T. Wearn, Professor of Medicine, Western Reserve University School of Medicine.

SECTION MEETINGS

APRIL 2—*Section of Dermatology and Syphilology.* Presentation of cases—a] City Hospital; b] New York Polyclinic Hospital; c] New York Hospital and Cornell Medical College; d] Miscellaneous cases. ¶ General discussion. ¶ Executive session. Nomination of Section Officers and one member of Advisory Committee.

APRIL 5—Section of Surgery. Reading of the minutes. ¶ Presentation of cases—a] A case of bilateral paralysis of inferior laryngeal nerve following thyroidectomy with spontaneous recovery, Henry F. Graham (by invitation); Discussion, William C. White; b] Parathyroid adenoma — multiple bone cyst formation, pathological fracture, cure following operation, Irwin E. Siris; Discussion, William Barclay Parsons; c] Carcinoma of the thyroid (2 cases), Frank B. Berry; Discussion, Howard A. Patterson; d] A case of hyperparathyroidism, Norman L. Higinbotham; Discussion, Bradley L. Coley. ¶ Papers of the evening—a] Cancer of the thyroid, William L. Watson, John Pool; Discussion, Frederic Bancroft, Arthur S. McQuillan; b] Recurrences in hyperthyroidism, Edwin B. Eckerson; Discussion, Morris K. Smith; c] The treatment of postoperative tetany, Francis M. Donehue; Discussion, Otto Pickhardt. ¶ General discussion. ¶ Executive session. Nomination of Section Officers and one member of Advisory Committee.

APRIL 9—*Section of Neurology and Psychiatry.* Reading of the minutes. ¶ Presentation of cases—a] A case of thromboangiitis obliterans with cerebral involvement, D. J. Impastato (by invitation); b] Postencephalitic palilalia and paliphraxia and forced singing (from the New York University Neuropsychiatric Division of Welfare Hospital), S. Bernard Wortis, Martin H. Stein (by invitation), Sidney Govons (by invitation). ¶ Papers of the evening—a] Neurospongioblastoma: clinical and pathological aspects, Joseph H. Globus; Discussion, Otto Marburg (by invitation), Lewis D. Stevenson; b] Further experience with cervical rib and the scalenus anterior syndrome, Russell Patterson; Discussion, Bronson Ray. ¶ Executive session. Nomination of Section Officers and one member of Advisory Committee.

APRIL 11—*Section of Pediatrics.* Executive session—a] Reading of minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Tachycardia in the new born, Herman Tarnower (by invitation); Discussion, Berton Lattin; b] Relationship of the jaws from birth to three years of age, J. H. Sillman, D.D.S. (by invitation); Discussion, Harry Bakwin; c] The use of sulfamethylthiazol in severe staphylococcic infections, Donald Weisman (by invitation); Discussion, Harry Neffson

(by invitation); d] Bacteriological and epidemiological distinctions between Grade A and Grade B pasteurized milk in New York City, Haven Emerson, representing the staff of the DeLamar Institute of Public Health of the College of Physicians and Surgeons, Columbia University. ¶ General discussion.

April 15—*Section of Ophthalmology.* Instruction hour — Neuro-ophthalmology, Kaufman Schlivek; Demonstration of slit lamp cases—Gordon M. Bruce, Girolamo Bonaccolto, Milton Berliner. ¶ Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Presentation of cases—a] Subacute dacryadenitis with fusiform bacillus conjunctivitis, Webb P. Chamberlain (by invitation); b] Plastic material for orbital implantation, Conrad Berens, Sidney Rothbard (by invitation); c] Autokeratoplasty, Wendell L. Hughes; Discussion, John C. Cunningham (by invitation); d] A simple suture for retention of corneal graft, Sigmund A. Agatston. ¶ Papers of the evening—a] Observations on the innervation and pharmacology of the eye muscles, Morris Bender (by invitation); b] Retrobulbar neuritis: an analysis of one hundred cases, Frank D. Carroll. ¶ General discussion.

April 16—*Section of Medicine.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Histamine in anaphylaxis and allergy, Laurence Farmer; b] Histaminase: Physiologic effects on man and its therapeutic value in medicine, Grace M. Roth, Ph.D., Mayo Clinic (by invitation); Bayard T. Horton, Mayo Clinic (by invitation); Discussion, David Perla. ¶ General discussion.

April 17—*Section of Genito-Urinary Surgery.* Executive session—a] Reading of minutes; b] Nomination of Section Officers and one member of Advisory Committee: For Chairman, John H. Morrissey; For Secretary, Frank C. Hamm; For Member of Advisory Committee, Simon A. Beisler; c] Election of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] A simplified method of nephropexy (motion picture), John Duff; Discussion, O. S. Lowsley; b] The genesis, diagnosis and treatment of urinary tuberculosis, Oscar Auerbach, Sea View Hospital (by invitation); William P. Herbst, Georgetown Medical School (by invitation); John L. Emmett, Mayo Clinic (by invitation). ¶ Discussion.

April 17—*Section of Otolaryngology.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Sphenoiditic hydrocephalus, Irving B. Goldman; Discussion, George A. Blakeslee; b] Pontofacial angle tumors with particular reference to involvement of the acoustic nerve, Joseph H. Globus; Discussion, Byron Stookey; c] Localized non-suppurative encephalitis of otorhinologic origin, Miles Atkinson (by invitation); Discussion, Emanuel D. Friedman, James G. Dwyer. ¶ General discussion.

April 19—*Section of Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Fascial transplants for abdominal paralysis, Nicholas Ransohoff; Discussion, Leo Mayer; b] Two-stage transplantation of the fibula for infected pseudarthrosis and congenital pseudarthrosis of the tibia, Philip Wilson; Discussion, John J. Nutt; c] Osteoid osteoma, Henry L. Jaffe; Discussion, A. Sumner Price. ¶ General discussion.

April 23—*Section of Obstetrics and Gynecology.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] The mental hygiene of preg-

nancy, labor and the puerperium, Margaret E. Fries; Discussion, Claude E. Heaton, Lawrence S. Kubie; b] Causes of death in carcinoma of the cervix uteri; an analysis of 124 autopsies in 1558 cases, Lionel S. Auster, Angelo M. Sala; c] The hormonal etiology of cervical carcinoma, Anthony Wollner.

AFFILIATED SOCIETIES

MARCH 18—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Presentation of cases. ¶ Papers of the evening—a] The shrunken pulmonary lobe, Oswald R. Jones (by invitation); b] The vanishing lung, Stanton T. Allison (by invitation). ¶ Discussion: ¶ Executive session.

MARCH 28—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case reports—a] Hemangioendothelioma of lung, Alfred Plaut; b] An unusual case of congenital heart disease, M. W. Johannsen. ¶ Papers of the evening—a] A consideration of so-called "granulosa" and "Theca" cell tumors of the ovary, Herbert F. Traut; b] Host-parasite relationships in some virus encephalitides, Lester S. King.

APRIL 15—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Presentation of cases. ¶ Papers of the evening—a] A simplified operation for Ménière's syndrome and for intractable pain in the distribution of the glosso pharyngeal and the trigeminal nerves, Abraham Kaplan (by invitation); b] An x-ray aid in the diagnosis of acute pylephlebitis (portal thrombosis), Anthony Bassler (by invitation); c] Case of pelvic actinomycosis treated by surgery and Roentgen ray, Harriet C. McIntosh, Maurice Rashbaum (by invitation); d] Motion picture: Roentgen kymographic studies of the movements of the small intestine and colon, George A. Weltz, Munich, Germany (by courtesy of Wendell G. Scott, St. Louis). ¶ Discussion, Foster Kennedy (by invitation); Maurice Rashbaum (by invitation). ¶ Executive session.

APRIL 25—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* Case reports—a] Torula infection of the central nervous system, Leo Wade (by invitation); b] Human tissue response to an unidentified microorganism resembling the bacillus lignieresi and past (pseudo-glanders), T. J. Curphey. ¶ Papers of the evening—a] Evaluation of postmortem bacteriology, Caspar G. Burn; b] Intracranial pathways for the extension of infection from the spheno-ethmoid sinuses, Rudolph Kramer (by invitation); Max L. Som (by invitation). ¶ Executive session.

DEATHS OF FELLOWS

COE, HENRY CLARKE: Clifton Terrace, Washington, D. C.; born in Cincinnati, Ohio, February 21, 1856; died in Washington, D. C., April 21, 1940; received the degrees of A.B. in 1878 and M.A. in 1881 from Yale University, M.D. from Harvard University Medical School in 1881 and from the College of Physicians and Surgeons, Columbia University, in 1882; M.R.C.S. (England) 1884; and L.R.C.P. (London) 1884; elected a Fellow of the Academy January 15, 1885.

Dr. Coe was emeritus professor of gynecology at New York University College of Medicine and at one time consulting gynecologist to the Bellevue, Woman's, Polyclinic, Beth Israel, St. Joseph's, Southside and Memorial Hospitals. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association and a member of the State and County Medical Societies.

During the World War, Dr. Coe served two years in foreign service as Colonel of the Medical Corps of the U. S. Army and was cited for distinguished service.

KRAETZER, ARTHUR FURMAN: 123 East 53 Street, New York City: born in Brooklyn, April 16, 1891; died in New York City, March 4, 1940; graduated in medicine from Cornell University Medical College in 1916; elected a Fellow of the Academy February 3, 1927.

Dr. Kraetzer was director of medicine at the Knickerbocker Hospital, associate attending physician to the Lenox Hill Hospital and attending physician to the thyroid out-patient-department at that institution. He was a Fellow of the American Medical Association and a member of the County and State Medical Societies.

RIGGS, AUSTEN FOX: Stockbridge, Massachusetts; born in Cassel, Germany, December 12, 1876; died in Stockbridge, March 5, 1940; received the degree of A.B. from Harvard University in 1898, M.D. from the College of Physicians and Surgeons, Columbia University, in 1902, and Sc.D. from Williams College in 1937; elected a Fellow of the Academy December 7, 1905.

Dr. Riggs was founder, medical director and president of the Austen Riggs Foundation; clinical professor of neurology at the College of Physicians and Surgeons, Columbia University; consulting psychiatrist to Vassar College (Poughkeepsie) and Williams College (Willamstown); and consulting neurologist to the House of Mercy Hospital at Pittsfield.

During the World War, Dr. Riggs recruited and commanded the American Relief Corps Ambulance No. 13 and after this country's entrance he served as a member of the Medical Advisory Board of the first and second selective military drafts. He was a lieutenant in the Medical Reserve Corps of the United States Army at his death.

Dr. Riggs was a diplomate of the American Board of Psychiatry and Neurology, a Fellow and life member of the American College of Physicians, a Fellow of the American Medical Association, a member of the American Neurological Association, the American Psychiatric Association, the National Committee on Mental Hygiene, and the Massachusetts and New York State Medical Societies.

Dr. Riggs was the author of "Just Nerves," "Intelligent Living," and "Play."

ROBERTS, DUDLEY DE VORE: 420 Lexington Avenue, New York City; born in Newark, New Jersey, March 1, 1874; died in New York City, March 9, 1940; graduated in Medicine from the College of Physicians and Surgeons, Columbia University, in 1898; elected a Fellow of the Academy January 2, 1919.

Dr. Roberts was consulting physician to the United States Marine Hospital at Stapleton, Staten Island, and a member of the American Gastro-Enterological Association.